NCGC National Clinical Guideline Centre

Psoriasis

Management of psoriasis

Clinical Guideline

Methods, evidence and recommendations

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1 Introduction

Psoriasis is an inflammatory skin disease that typically follows a relapsing and remitting course. It is associated with joint disease in a significant proportion of people.

1.1 Epidemiology

The prevalence is estimated to be around 1.3-2.2%[1] in the UK, with the greatest prevalence being in white people. Men and women are equally affected. It can occur at any age although is uncommon in children (0.71%) and the majority of cases occur before the age of 35 years.

1.2 Clinical features

Plaque psoriasis is by far the commonest form of the condition (90% of people with psoriasis) and is characterised by well delineated red, scaly plaques[1]. The extent of involvement is variable, ranging from a few localised patches at extensor sites, to generalised involvement involving any site. Rarely, psoriasis may involve the whole body, erythroderma. The appearance of plaque psoriasis may be modified by site. Flexural (also known as inverse or intertriginous) psoriasis refers to plaque psoriasis at submammary, groin, axillary, genital and natal cleft sites, and is typically less scaly. Seborrhoeic psoriasis ('sebopsoriasis') is similar in appearance and distribution to seborrhoeic dermatitis (hence the name) and may occur in isolation or associated with plaque psoriasis elsewhere. Other types of psoriasis include guttate psoriasis (an acute eruption of small (< 1 cm) papules of psoriasis which appear over a period of a month or so and is preceded by a streptococcal infection in around 2/3rd of people), and pustular psoriasis which includes generalised pustular psoriasis (GPP) and localised forms (ie: palmoplantar pustulosis and acrodermatitis continua of Halopeau). Distinctive nail changes occur in around 50% of all those affected and are more common in those with arthritis. Occasionally combinations of the different types develop simultaneously or sequentially over time in the same person. **Plaque** psoriasis is usually the type referred to by both health care professionals and patients when using the term 'psoriasis'[2]. Unless stipulated otherwise, the term psoriasis refers to plaque psoriasis in this guideline. The phrase ***'difficult-to-treat sites'*** encompasses the face, flexures, genitalia, scalp, palms and soles and are so-called because psoriasis at these sites are especially high impact and/or result in functional impairment, require particular care when prescribing topical therapy and/or be resistant to treatment.

1.3 Disease Impact

Death directly due to psoriasis is rare, but the chronic, incurable nature of psoriasis means that associated morbidity is significant. People with psoriasis, like those with other major medical disorders, have reduced levels of employment and income as well as a decreased quality of life. The impact of psoriasis encompasses functional, psychological, and social dimensions[3]. Factors that contribute to this include symptoms specifically related to the skin (for example, chronic itch, bleeding, scaling and nail involvement), problems related to treatments (mess, odour, inconvenience and time), arthritis, and the effect of living with a highly visible, disfiguring skin disease (difficulties with relationships, difficulties with securing employment and poor self esteem). Even people with minimal involvement (less than the equivalent of three palm areas) state that psoriasis has a major effect on their life. The combined costs of long-term therapy and social costs of the disease have a major impact on healthcare systems and on society in general. About a third of people with psoriasis experience major psychological distress, and the extent to which they feel socially stigmatised and excluded is substantial[4]. Healthcare professionals, including dermatologists, often fail to appreciate the extent of this disability and even when it is correctly identified, some estimates suggest that fewer than a third of people with psoriasis receive appropriate psychological interventions.

1.4 Comorbidities

Aside from the burden of arthritis, and psychological morbidity, a number of studies have suggested that people with psoriasis may also be at risk of cardiovascular disease. It is unclear whether this increase directly relates to the psoriasis itself, or an increased incidence of traditional cardiovascular risk factors reported in people with psoriasis[5,6]. Risk factors include obesity, type 2 diabetes mellitus, metabolic syndrome, excess alcohol intake or alcoholism, smoking and hyperlipidaemia (which may be partly iatrogenic due to agents such as ciclosporin and acitretin). Community- and hospital-based studies suggest that people with psoriasis, particularly those with severe disease, may also be at increased risk of lymphoma and non-melanoma skin cancer. The relative influence of known confounders such as concomitant therapy with immunosuppressants, phototherapy, smoking, and alcohol is unclear.

1.5 Approach to Management

The significant impact of psoriasis on well being suffered by affected individuals, underlines the need for prompt, effective treatment, and long-term disease control. Treatments available for psoriasis are varied. For the purposes of this guideline, ***first line therapy*** describes the traditional topical therapies (such as corticosteroids, vitamin D and analogues, dithranol and tar preparations). ***Second line therapy*** includes phototherapy, broad- or narrow-band ultraviolet [UV] B light, with or without supervised application of complex topical therapies such as dithranol in Lassar's paste or crude coal tar and photochemotherapy, psoralen plus UVA light [PUVA], and non-biological systemic agents such as ciclosporin, methotrexate and acitretin. ***Third line therapy*** refers to systemic biological therapies that use molecules designed to block specific molecular steps important in the development of psoriasis such as the TNF antagonists adalimumab, etanercept and infliximab, and ustekinumab, anti-IL12-23 monoclonal antibody[7-10]. These agents are approved for use by NICE, subject to certain disease severity criteria, and acquisition costs are high. All of these interventions can be associated with long-term toxicity and some people with psoriasis have treatment-resistant disease.

The approach to therapy is, to a large degree, governed by the extent and severity of disease. In general, people whose disease is localised to <3% body surface area or 3 palms worth, which comprises the vast majority of people affected with psoriasis[11], can be managed with topical therapy alone. Adherence to topical therapy regimens may be the greatest barrier to effective disease control, and attention to cosmetic acceptability, formulation, local side effect profiles, and practicalities of application is important. In people with psoriasis that is extensive, where topical therapy would be impractical or ineffective or that is associated with psoriatic arthritis, second line therapies tend to be used. Recent guidelines from the British Association of Dermatologists (which are in line with NICE guidance and the UK marketing authorisation for these drugs)[2] recommend that third-line biological therapies should be generally reserved for people with severe disease for whom second line treatments have failed or cannot be used. There are important exceptions to this general over view however, as even localised disease can be resistant to treatment and may have a very significant impact on patients' functional, psychological or social well being, such that escalation to second line or even third line therapy is appropriate. Equally, some people with extensive disease, will only seek advice and be interested in treatments for localised sites that are especially bothersome, for example, visible sites such as the face or backs of hands. Setting aside psoriatic arthritis, there is no compelling evidence that any of the interventions have a disease modifying effect or impact beyond improvement of the psoriasis itself and so, with the exception of the minority of patients with unstable and life threatening forms of psoriasis, the approach to therapy and risk/benefit assessment of the different interventions is strongly influenced by the impact the psoriasis is having on the well being of the individual affected.

1.6 Service configuration and pathways of care

Most people with psoriasis are managed in primary care[12]; specialist referral is required in up to 60% at some point in their disease course[13]. These data are based on adult populations, but approach to care in children and young adults is similar. Commonly cited triggers for referral to secondary care include: diagnostic uncertainty; request for further counselling or education including demonstration of topical treatment; failure to respond to appropriately used topical therapy for three months; psoriasis at sites that are difficult to treat and/or at high impact sites; if unresponsive to initial therapy; adverse reactions to topical therapies; need for systemic therapy, phototherapy, day treatment, or inpatient admission; disability preventing work or excessive time off work; significant psychosocial disability; presence of psoriatic arthritis and; life threatening forms of psoriasis where urgent referral may be justified.

Ongoing supervision of those on systemic therapy occurs in specialist settings, sometimes with shared care arrangements for drug monitoring in primary care. Supra-specilaist (level 4, tertiary) centres with access to multidisciplinary teams with experience in complex interventions and associated multi-morbidities provide specialist care for the minority of people. A recent UK audit in the adult population demonstrated wide variations in practice, and in particular, access to specialist treatments (including biologics), appropriate drug monitoring, specialist nurse support and psychological services[14]. No comparable audit has been carried out in children. Recommended indications for referral from primary to specialist care have been published[15] but there are no formal standards/indications for supra-specialist level care (level 4).

Delivery of care in all specialist (level 3 and 4) settings[12] largely follows the traditional model of outpatient consultations with daycare/inpatient admission for more severe disease. People on biological therapy attend secondary or tertiary care centres for monitoring whilst the drug itself is delivered by community based companies.

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be accessible to people with additional needs and culturally appropriate. Families and carers should also be given the information and support they need.

1.7 Psoriasis in chidren and young people

Psoriasis in childhood is less common than adults. It tends to present in later childhood with a median age of onset between 7 and 10 years and an estimated UK prevalence of 0.71%[16-19]. Since one third of adult patients with psoriasis present before 20 years of age they are an important group to consider in the overall disease management[20]. A positive family history of psoriasis is associated with a reduced age of onset of the disease[21,22].

Paediatric practice tends to mirror that in adults, and in this guideline, recommendations relate to everyone with psoriasis irrespective of age, unless otherwise stated. Where relevant, the term children refers to those up to 12 years, and young people thereafter, merging with the adult population by 18 years of age. Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with psoriasis. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Points of particular relevance to the paediatric population include the following:

- Plaque type psoriasis is also the commonest form in the paediatric population. Other forms are guttate psoriasis with relapses following infections[23] and in very young children, less than two

years of age, napkin psoriasis. This typically affects the inguinal folds and then spreads to involve the trunk and limbs[24].

- As with any condition occurring in children and young people, psoriasis may impact on the person's psychological and emotional development and educational needs, and these aspects need to be considered in context of the individual, family and carers.
- There is a lack of data on interventions in children and young people with psoriasis. The GDG agreed to base treatment recommendations on RCTs with extrapolation to children if no separate paediatric evidence was found. Any exceptions to this principle are noted in the LETR tables of the relevant review questions. Note that only two studies[24,25] that specifically addressed psoriasis in children were identified and included in the guideline.
- Psoriasis in children and young people is currently managed as part of the general paediatric dermatology case mix by consultant dermatologists who also care for children. There are no specialised paediatric psoriasis clinics although combined paediatric dermatology and rheumatology clinics are in existence in some centres to manage psoriasis and psoriatic arthritis in children. Due to the drug licensing restrictions, children with relatively mild disease are often referred to secondary care for treatment.
- Most topical agents have licensing restrictions from specific ages and systemic therapies are currently not licensed for the treatment of psoriasis in children of less than 16 years of age apart from Etanercept (the only biological therapy currently licensed for children of less than 16 years of age). Ultimately the prescriber must take responsibility for using drugs outside of their licensed indications but it is important to involve the parents and, if possible the child, in a discussion about risks and potential benefits, especially when considering interventions such as PUVA and systemic drugs. In all discussions with patients about their treatment the clinician should establish that the patient has the capacity[26] to make a fully informed decision about their care, and the ability to understand the potential benefits (and risks) of treatment.
- In the case of children, clinicians would normally involve those with parental responsibility in the clinical decision-making process. Clinicians should also consider the maturity and competence of the child to understand and make decisions about their own care. Children can consent to treatment when they are able to understand the risks and benefits but they cannot legally refuse treatment against their parents' wishes until they are 16 years old. It is important to consider the young person's cognitive developmental stage when discussing the disease and treatment options. Using appropriate terminology will help children and young people participate actively in decision-making.
- As children mature into young people and adults they should be encouraged to take more responsibility for managing their condition. Arrangements for transition to adult care (e.g. joint clinics with adult and paediatric dermatology teams) should be an integral part of the service. The relevant principles are considered in a Department of Health publication[27].
- When managing psoriasis in children and young people, treatment choice should be carefully considered to avoid or minimise long-term sequelae. This aspect is especially pertinent in relation to phototherapy.

1.8 Aims of the Guideline

Psoriasis is a common, chronic disease, which for many people, is associated with profound functional, psychological and social morbidity and important co-morbidities. Effective treatments are available. Some treatments are expensive; all require appropriate monitoring and some may only be accessed in specialist care settings. Evidence indicates that a substantial proportion of people with psoriasis are currently dissatisfied with their treatment.

This guideline aims to provide clear recommendations on the management of psoriasis for all people with psoriasis. The diagnosis of psoriasis has not been included within the scope, partly for pragmatic reasons given that to cover psoriasis management itself is a considerable task, but also because there are no agreed diagnostic criteria or tests available and accurate diagnosis remains primarily a clinical one. In considering which specific aspects of psoriasis management to address, the guideline development group have focussed on areas most likely to improve the management and delivery of care for a majority of people affected, where practice is very varied and/or where clear consensus or guidelines on treatments are lacking. We have therefore addressed how to holistically assess people with psoriasis at all stages in the treatment pathway, the use of first, second and third line interventions and when to escalate therapy, and the role of psychological interventions and self management strategies. We have avoided categorical description of what constitutes particular levels of disease severity, for example 'mild' or 'moderate and severe' excepting disease severity criteria for plaque psoriasis already described by NICE in order to qualify for biological therapy. There are no widely accepted definitions that are applicable to all situations and it is a contentious subject. Instead we emphasise the importance of measuring disease severity and impact to individualise care, and plan and evaluate management. There are also a number of key areas that we have not addressed for a variety of reasons. First, we have not evaluated the role of emollients in the treatment of psoriasis. These are widely prescribed and clinical experience suggests that they are used with benefit by patients. In the absence of robust RCT or high quality studies to inform recommendations to change this practice, and the fact that all placebo controlled trials involving topicals use a vehicle (which will have emollient properties) in the placebo arm, the treatment pathway starts on the assumption that when appropriate, emollients have already been prescribed. Secondly, we have not included fumaric acid esters in our evaluation of second line therapies. This intervention is not licensed for any indication in the UK and therefore cannot be included.

We sincerely hope that these guidelines facilitate the delivery of high quality health care and improve outcomes for people with psoriasis.

2 Patient experience of living with psoriasis

From a patient's perspective psoriasis does not discriminate. It is, at best, an inconvenient disease, at worst, a living nightmare. Psoriasis can be a relentless 24 hours a day, 7 days a week, 365 days of the year problem. A battle between treating flaky, sore skin and attempting to carry on a daily routine of normal life of employment, family, social events and general day-to-day activities that those who do not have psoriasis take for granted. It is a relentless condition which has a detrimental impact on quality of life yet for which many people have given up seeking medical support[28].

The grinding process of a skin which is shedding and its treatment are just part of living with the condition. There are other considerations that people with psoriasis soon learn are part and parcel of having such a visible disease. The stare which lingers just too long and the look of revulsion are quickly learnt. Then there are the awkward silences in situations when psoriasis is first encountered by someone new such as during a routine visit to the hairdresser; the constant justification of 'it's not contagious' or 'it's just psoriasis' are responses the person living with it will have ready to say on every occasion close scrutiny appears imminent. And so, unwittingly, an undermining habit of self justification is acquired.

The impact of psoriasis on an individual's life varies enormously, whether newly diagnosed or after many years of active disease. The newly diagnosed are often bewildered by the statement "you have psoriasis" as that (for many) is often the start of a quest to find answers to more questions which cannot possibly be answered in the few minutes of a first consultation. The words and advice from a medical professional at that initial appointment will remain with the person affected for the rest of their long life with psoriasis.

What is said, read or learnt will have a great impact and may shape an individual's approach to how they live their lives in the future. A few careless words at the wrong time or unrealistic advice may have profound consequences leaving an individual with false hope about the effectiveness of treatment or desperation at the thought of a disease with which they have been burdened.

Dealing with an individual's psoriasis needs runs much deeper than providing a prescription. That is only part of the solution. Effective treatment is, of course, important but psoriasis' impact can shatter self-confidence. It is a lonely disease as treatments are usually self-administered and time consuming. A lifetime of applying ointments, swallowing pills or injecting drugs lies ahead. In a busy household, treatment time may not always be available. The person with psoriasis may have to fit around others which can cause friction and irritation. The mess associated with a shedding skin, the odour of treatments and their ability to stick to clothing can cause acute embarrassment and difficulties within relationships.

Psoriasis is an invidious condition which needs to be taken seriously. The joint ongoing management of psoriasis between patient and healthcare provider on every aspect of this disease will not remove its physical and emotional burden but might improve the outcomes.

3 Development of the guideline

3.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- the quick reference guide (QRG) presents recommendations in a suitable format for health professionals
- information for the public ('understanding NICE guidance' or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

3.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

- The Department of Health has asked NICE: 'to produce a clinical guideline on the management of psoriasis'.

3.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Catherine Smith in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every four weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, research fellows, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

3.4 What this guideline covers

Groups covered in this guideline are children and adults with a diagnosis of psoriasis. Consideration is given to the specific needs, if any, of people with psoriatic arthritis.

Key clinical issues covered:

- Evaluation of disease severity and impact on people with psoriasis.
- Identification of psoriatic arthritis.
- Management of psoriasis including, for example:
  - topical therapy:
    - corticosteroids
    - vitamin D analogues
    - coal tar (with or without phototherapy)
    - dithranol (with or without phototherapy)
  - phototherapy (narrow band UVB)
  - photochemotherapy (psoralen and UVA)
  - systemic therapy:
    - ciclosporin
    - methotrexate
    - acitretin.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

- Self-management.
- Management of the psychological impact of psoriasis.
- Combination and sequencing of treatments.

For further details please refer to the scope in Appendix A and review questions in section 4.1.

3.5 What this guideline does not cover

Groups not covered in this guideline are children and adults who do not have a diagnosis of psoriasis.

Key clinical issues not covered:

- Diagnosis.
- Management of psoriatic arthritis.
- Complementary and alternative treatments.
- Fumaric acid esters[a].

3.6 Relationships between the guideline and other NICE guidance

Health Technology Appraisals to be incorporated in this guidance:

- Ustekinumab for the treatment of adults with moderate to severe psoriasis. NICE technology appraisal guidance 180 (2009). Available from www.nice.org.uk/guidance/TA180
- Adalimumab for the treatment of adults with psoriasis. NICE technology appraisal guidance 146 (2008). Available from www.nice.org.uk/guidance/TA146
- Infliximab for the treatment of adults with psoriasis. NICE technology appraisal guidance 134 (2008). Available from www.nice.org.uk/guidance/TA134
- Etanercept and efalizumab for the treatment of adults with psoriasis. NICE technology appraisal guidance 103 (2006). Available from www.nice.org.uk/guidance/TA103

Related NICE Health Technology Appraisals:

- Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. NICE technology appraisal guidance 199 (2010). Available from www.nice.org.uk/guidance/TA199

Related NICE Interventional Procedures:

- Grenz rays therapy for inflammatory skin conditions. NICE interventional procedure guidance 236 (2007). Available from www.nice.org.uk/guidance/IPG236

Related NICE Clinical Guidelines:

- Alcohol-use disorders: physical complications. NICE clinical guideline 100 (2010). Available from www.nice.org.uk/guidance/CG100
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Obesity. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43

a Fumaric acid esters are not licensed for any indication within the UK and therefore we are not able to consider this treatment within the guideline

Related NICE Public Health Guidance:

- Alcohol-use disorders – preventing harmful drinking. NICE public health guidance 24 (2010). Available from www.nice.org.uk/guidance/PH24
- Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10

4 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009 [29]

4.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention or experimental reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy, and population, presence or absence of risk factors and list of ideal minimum confounding factors for reviews of prognostic factors. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). Further information on the outcome measures examined follows this section. For all interventions that were reviewed, absolute rates of efficacy and toxicity were also sought in order to provide information for people with psoriasis and their healthcare providers in line with the Patient Experience guideline[30], which recommends that information is provided as a natural frequency using the same denominator and with intervention and control rates quoted separately. For this, efficacy data were based on the numbers achieving either PASI75 or clear/nearly clear on the PGA, whichever outcome was available or provided the largest sample size. Similarly, for toxicity, this was reported for withdrawals due to adverse events and the adverse events specified for that intervention.

Chapter	Review questions	Outcomes
Assessment	In people with psoriasis (all types), which are the most effective tools to assess the (a) severity and (b) impact of disease across all levels of healthcare provision and at any stage of the disease journey?	• Construct validity – convergent and divergent • Inter-rater reliability • Intra-rater reliability • Internal consistency • Repeatability • Practicability • Sensitivity to change
Assessment	In people with psoriasis (all types), which is the most accurate diagnostic tool compared with clinical diagnosis by a rheumatologist to help a non-specialist identify psoriatic arthritis?	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • Likelihood ratios
Assessment	In people with psoriasis (all types) and suspected psoriatic arthritis, how quickly should referral to a specialist be made in order to minimise the impact of disease on symptoms, joint damage and quality of life?	• Quality of life : HAQ, EQ5D • Disease symptoms/signs: pain, tenderness, joint swelling (or second-line therapy as a surrogate) • Joint damage: clinical, radiological (e.g. Sharp, Larsen, Steinbrocker) • Biochemical markers : CRP and ESR • Mortality • Cardiovascular events
Assessment	Are people with psoriasis at higher risk than people without psoriasis for significant comorbidities and	• Incidence of comorbidities

Chapter	Review questions	Outcomes
	are there subgroups within the psoriasis population at a further increased risk?	• Incidence of mortality
Assessment	In people with psoriasis (all types) who have been exposed to coal tar, phototherapy (BBUVB, NBUVB and PUVA), systemic therapy (non-biological and biological therapy), what is the risk of skin cancer compared with people not exposed to these interventions and which individuals are at particular risk?	• Melanoma skin cancer • Non melanoma skin cancer (stratified as squamous cell carcinoma and basal cell carcinoma)
Topicals	In people with chronic plaque psoriasis of the trunk and/or limbs, what are the clinical effectiveness, safety, tolerability, and cost effectiveness of topical vitamin D and vitamin D analogues, potent or very potent corticosteroids, tar, dithranol and retinoids compared with placebo or vitamin D and vitamin D analogues, and of combined or concurrent vitamin D and vitamin D analogues and potent corticosteroids compared with potent corticosteroid or vitamin D and vitamin D analogues alone?	• Clear/nearly clear or marked improvement (at least 75% improvement on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)) • Clear/nearly clear or marked improvement (at least 75% improvement on Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment) • Percentage change in PASI • Change in DLQI • Duration of remission • Time-to-remission or time-to-maximum effect • Withdrawal due to toxicity • Withdrawal due to lack of efficacy • Skin atrophy
Topicals	In people with psoriasis at high impact or difficult-to-treat sites (scalp, flexures, face), what are the clinical effectiveness, safety, tolerability and cost effectiveness of vitamin D and vitamin D analogues, mild to very potent corticosteroids, combined or concurrent vitamin D or vitamin D analogue and potent corticosteroid, pimecrolimus, tacrolimus, tar, dithranol and retinoids compared with placebo, corticosteroids or vitamin D or vitamin D analogues.	• Clear/nearly clear or marked improvement (at least 75% improvement on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)) • Clear/nearly clear or marked improvement (at least 75% improvement on Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment) • Percentage change in PASI • Change in DLQI • Duration of remission

Chapter	Review questions	Outcomes
		• Time-to-remission or time-to-maximum effect • Withdrawal due to toxicity • Withdrawal due to lack of efficacy • Skin atrophy
Phototherapy	In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of BBUVB, NBUVB and PUVA compared with each other or placebo/no treatment?	• PASI75 • PASI50 • Change in PASI • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA) • Relapse (time-to-event data if available otherwise ordinal data accepted) • Time (or number of treatments) to remission/max response • Change in DLQI • Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved) • Cataracts
Phototherapy	In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of acitretin plus UVB (NBUVB and BBUVB) and acitretin plus PUVA compared with their monotherapies and compared with each other?	• PASI75 • PASI50 • Change in PASI • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA) • Relapse (time-to-event data if available otherwise ordinal data accepted) • Time to remission/maximum response • Change in DLQI • Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved) • Cataracts • Number of UV treatments (as a surrogate for cumulative dose)
Phototherapy	In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of UVB (NBUVB or BBUVB) combined with dithranol, coal tar or vitamin D and vitamin D analogues compared with UVB alone or topical therapy alone?	• PASI75 • PASI50 • Change in PASI (mean improvement); • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA); • Relapse (time-to-event data if available otherwise ordinal data accepted) • Time to remission/max response; • Change in DLQI

Chapter	Review questions	Outcomes
		• Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved); • Cataracts; • Number of UV treatments (as a surrogate for cumulative dose)
Systemic therapy (second-line, non-biological)	In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of systemic methotrexate, ciclosporin and acitretin compared with each other or with placebo?	• PASI75 • PASI50 • Change in PASI • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA); • Improvement (for PPP) • Relapse (time-to-event or relapse rate as a surrogate measure) • Time to remission/maximum response • Change in DLQI • Severe adverse events: Methotrexate (MTX): hepatotoxicity, marrow suppression and pneumonitis Acitretin: hyperlipidaemia, hepatotoxicity, skeletal AEs and cheilitis Ciclosporin (CSA): renal impairment, hypertension, gout and hyperuricaemia • Withdrawal due to toxicity
Methotrexate and risk of heptotoxicity	In people with psoriasis (all types) who are being treated with methotrexate, are there specific groups who are at high risk of hepatotoxicity?	• Biopsy grade • Biopsy grade progression • Periportal inflammation • Fatty change • Fibrosis • Cirrhosis • Abnormal liver function tests
Methotrexate and monitoring for hepatotoxicity	In people with psoriasis (all types) who are being treated with methotrexate or who are about to begin treatment with methotrexate, what is the optimum non-invasive method of monitoring hepatotoxicity (fibrosis or cirrhosis) compared with liver biopsy?	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • Likelihood ratios
Sequencing of biological therapy	In people with chronic plaque psoriasis eligible to receive biologics, if the first biological fails, which is the next effective, safe and cost effective strategy?	• PASI75 • PASI50 • Change in PASI • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA); • Relapse (time-to-event data if available otherwise ordinal data

Chapter	Review questions	Outcomes
		accepted) • Time to remission/maximum response • Change in DLQI • Severe adverse events • Withdrawal due to toxicity
Cognitive behavioural therapy	In people with psoriasis (all types), how effective are cognitive behavioural therapy (group and individual) interventions alone or as an adjunct to standard care compared with standard care alone for managing psychological aspects of the disease in reducing distress and improving quality of life?	• Reduced distress/anxiety/depression (change in Hospital Anxiety and Depression Scale (HADS)/Beck Depression Inventory (BDI)/Speilberger State Trait Anxiety Inventory (STAI)) • Reduced stress (change in Psoriasis Life Stress Inventory (PLSI)) • Improved quality of life (change in Dermatology Life Quality Index (DLQI)/Psoriasis Disability Index (PDI)) • Reduced psoriasis severity (change in PASI)
Self-management	What strategies can best support people with psoriasis (all types) to self-manage the condition effectively?	• Patient satisfaction • Concordance with treatment • Reduced distress/anxiety/depression (change in HADS) • Reduced disease severity (change in PASI) • Reduced stress (PLSI) • Improved quality of life (change in DLQI/PDI) • Service use

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual [2009] [29]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. Additional subject specific databases were used for some questions: e.g. PsycInfo for patient views. All searches were updated on 8th March 2012. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a topic-specific search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

4.2.11 Call for evidence

The GDG decided to initiate a 'call for evidence' for comparative data to address the question of whether biologics are safe and effective in people with chronic plaque psoriasis who have previously received another biological agent, as they believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence.

4.2.12 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to psoriasis in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2008, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D. All searches were updated on 8th March 2012. No papers published after this date were considered.

4.3 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C.
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual[29].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix H.
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
    - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
    - Observational studies: data presented as a range of values in GRADE profiles
    - Diagnostic studies: data presented as a range of values in adapted GRADE profiles and a narrative summary is provided

- Prognostic studies: data presented as a range of values in summary tables, with matrices for study quality

4.3.1 Inclusion/exclusion

See the review protocols in Appendix C for full details. The GDG were consulted about any uncertainty regarding the inclusion/exclusion of selected studies. Note that this guideline did not consider the management of psoriatic arthritis; therefore, studies that were primarily designed to investigate psoriatic arthritis rather than psoriasis affecting the skin were excluded. This was defined as studies primarily designed to treat the joint rather than the skin component of the disease and in a rheumatology rather than dermatology setting. However, studies were not excluded on the basis of the proportion of participants with PsA alone.

The GDG agreed that in most situations it would be reasonable to extrapolate data from adult populations to children when there was no or little data. Therefore, the GDG agreed to base treatment recommendations on RCTs with extrapolation to children if no separate paediatric evidence was found. Any exceptions to this principle will be noted in the LETR tables of the relevant review questions. Note that only two studies[24,25] that specifically addressed psoriasis in children were identified and included in the guideline.

Regarding the different phenotypes of psoriasis, unless otherwise stated, data were sought for all types of psoriasis and reported separately if available. Plaque psoriasis is the commonest form of the condition (90% of patients) and is usually the type referred to by both health care professionals and patients when using the term ‘psoriasis’. Other types of psoriasis include guttate psoriasis, pustular psoriasis which includes generalised pustular psoriasis and localised forms (ie: palmoplantar pustulosis and acrodermatitis continua of Halopeau) and nail psoriasis. Unless stipulated otherwise, the term psoriasis refers to plaque psoriasis in this guideline; where recommendations relate to types of psoriasis other than chronic plaque disease, the subtype of psoriasis is stated in the recommendation. Psoriasis in all its forms can be modified by site. The phrase 'difficult-to-treat sites' encompasses the face, flexures, genitalia, scalp, palms and soles. Psoriasis at these sites is especially high impact and/or may result in functional impairment, require particular care when prescribing topical therapy and may be very resistant to treatment.

4.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: clear/nearly clear or marked improvement, PASI90, PASI75, relapse, withdrawal due to toxicity, withdrawal due to lack of efficacy, skin atrophy, burn, cataracts, severe adverse events, concordance with treatment and service use. The continuous outcomes: change in PASI, change in DLQI, duration of remission, number of UV treatments, time (or number of treatments) to remission, change in Hospital Anxiety and Depression Scale (HADS)/Beck Depression Inventory (BDI)/Speilberger State Trait Anxiety Inventory (STAI), change in Psoriasis Life Stress Inventory (PLSI), change in Psoriasis Disability Index (PDI), change in HADS, change in Psoriasis Life Stress Inventory (PLSI) were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Change scores were reported where available for continuous outcomes in preference to final values. However, if only final values were available, these were reported and meta-analysed with change scores. Where reported, time-to-event data were presented as a hazard ratio.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at p<0.1 or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out sensitivity analysis based on the risk of bias of the studies if there were differences in study limitations, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases when significant heterogeneity was not explained by the abovementioned sensitivity analyses, we carried out predefined subgroup analyses as specified in the review protocols.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes for each intervention group were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error for the mean difference between groups was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if p value was reported as "p ≤0.001", the calculations for standard deviations would be based on a p value of 0.001. If these statistical measures were not available then the available data were reported in a narrative style but not included in the meta-analysis.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Network meta-analysis was conducted for the review questions on the topical therapies for chronic plaque psoriasis at the trunk and limbs and high impact/difficult-to-treat sites. This allowed indirect comparisons of all the drugs included in the review when no direct comparison was available.

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS19. We used a multi-arm random effects model template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between arms in trials with any number of trial arms. The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo Simulation.

Networks of evidence were developed and analysed based on the following binary outcomes:

- Clear/nearly clear or marked improvement (at least 75% improvement) on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)
- Clear/nearly clear or marked improvement (at least 75% improvement) on Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment

The odds ratios were calculated and converted into relative risks for comparison to the direct comparisons. The ranking of interventions was also calculated based on their relative risks compared to the control group. For details on the methods of these analyses, see Appendix K and Appendix L.

Data synthesis for prognostic factor reviews

Odds ratios, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers. Data were not combined in a meta-analysis for

observational studies. Sensitivity analyses were carried out on the basis of study quality and results were reported as ranges.

Data synthesis for diagnostic test accuracy reviews

For diagnostic test accuracy studies, the following outcomes were reported: sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and pre- and post-test probabilities. In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data to allow calculation of these accuracy measures. Where possible the results for sensitivity and specificity were presented using Cochrane Review Manager (RevMan5) software.

Data synthesis for diagnostic test validity and reliability review

For investigating test validity and reliability of scales recording the severity and impact of psoriasis, the following outcomes were reported: Convergent validity, discriminate validity, internal consistency, inter-rater reliability, intra-rater reliability, practicability and sensitivity to change. Appropriate statistics were reported for each of these outcomes with their 95% confidence intervals or standard deviations for mean values where possible: Pearson product-moment correlation coefficient, Spearman rank correlation coefficient, kappa statistics, intra-class correlation, internal consistency coefficients (Crohnbach's alpha) and time to administer the test. Data were summarised across outcomes and comparisons in a tabular format and any heterogeneity was assessed.

4.3.3 Type of studies

For most intervention evidence reviews in this guideline, randomised controlled trials (RCTs) were included. Where the GDG believed RCT data would not be appropriate this is detailed in the protocols in Appendix C. RCTs were included as they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects.

For diagnostic evidence reviews, diagnostic cohorts and case controls studies were included and for prognostic reviews cohort studies were included.

4.3.4 Types of analysis

Estimates of effect from individual studies were based on a modified available case analysis (ACA) where possible or on an intention to treat (ITT) analysis if this was not possible.

ACA analysis is where only data that was available for participants at the follow-up point is analysed, without making any imputations for missing data. In the modification for binary outcomes, participants known to have dropped out due to lack of efficacy were included in the denominator for efficacy outcomes and those known to have dropped out due to adverse events were included in the numerator and denominator when analysing adverse events. This method was used rather than intention-to-treat analysis to avoid making assumptions about the participants for whom outcome data were not available, and rather assuming that those who drop out have the same event rate as those who continue. This also avoids incorrectly weighting studies in meta-analysis and over-estimating the precision of the effect by using a denominator that does not reflect the true sample size with outcome data available. If there was a high drop-out rate for a study then a sensitivity analysis was performed to determine whether the effect was changed by using an intention-to-treat analysis. If this was the case both analyses would be presented.

ITT analysis is where all participants that were randomised are considered in the final analysis based on the intervention and control groups to which they were originally assigned. It was assumed that participants in the trials lost to follow-up did not experience the outcome of interest (categorical outcomes) and they would not considerably change the average scores of their assigned groups (for

continuous outcomes). It is important to note that ITT analyses tend to bias the results towards no difference. ITT analysis is a conservative approach to analyse the data, and therefore the effect may be smaller than in reality.

4.3.5 Unit of analysis

This guideline includes RCTs with different units of analysis. Some studies randomised individual participants to the intervention (parallel or between-patient studies) while others randomised body halves to the intervention (within-patient studies, analogous to crossover trials).

It was recognised that data from within-patient trials should be adjusted for the correlation coefficient relating to the comparison of paired data. Therefore, if sufficient data were available, this was calculated and the standard error was adjusted accordingly.

Additionally, within- and between-patient data were pooled, accepting that this may result in underweighting of the within-patient studies; however, it is noted that this is a conservative estimate. Sensitivity analyses were undertaken to investigate whether the effect size varied consistently for within- and between-patient studies and there was no evidence that the size of effect varied in a systematic way.

4.3.6 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational intervention studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as one table in the guideline (called clinical evidence profiles). This includes the details of the quality assessment pooled outcome data, and where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the study arm sample sizes for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N across studies: sum of the number of patients with events divided by sum of number of patients) are shown with percentages. This is for information only and is not intended to show pooling (which was performed using a weighted meta-analysis as described above). Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 2. The main criteria considered in the rating of these elements are discussed below (see section 4.3.7 Grading the quality of clinical evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 3: The GRADE toolbox is currently designed only for randomised trials and observational intervention studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Table 1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate

Quality element	Description
	of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.7 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias were rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 4.3.8 to 4.3.11.

4.3.18 Study limitations

The main limitations for randomised controlled trials are listed in Table 4.

The GDG accepted that participant blinding in psychological or educational intervention studies was impossible. Nevertheless, open-label studies for cognitive behavioural therapy and self-management were downgraded to maintain a consistent approach in quality rating across the guideline and in recognition that some of the important outcomes considered were subjective or patient reported (patient satisfaction, reduced distress/anxiety/depression, improved quality of life (change in DLQI/PDI) and therefore highly subjected to bias in an open label setting.

Table 4: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials

Evidence for diagnostic data was evaluated by study, using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists. Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 1):

- Patient selection
- Index test
- Reference standard
- Flow and timing

Figure 1: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Source: University of Bristol –QUADAS-2 website (http://www.bris.ac.uk/quadas/quadas-2)

For prognostic studies, quality was assessed using a modified version of the Checklist for Prognostic Studies (NICE Guidelines Manual, 2009[29]). The quality rating was derived by assessing the risk of bias across 5 domains (selection bias; attrition bias; prognostic factor bias; outcome bias; and confounders and analysis bias, with outcome measurement and confounders being assessed per outcome). GRADE profiles were not used as the information regarding the quality of the evidence, which was not combined in a meta-analysis, was more clearly presented for ease of interpretation by using a quality matrix that clearly shows the limitations of each study.

For validity and reliability studies the quality was rated according to the following domains relevant for each outcome. Note that study size was not considered in the quality rating but was taken into account by the GDG when assessing the data. Applicability was considered for all outcomes in terms of how the tests were analysed (dichotomised/categorised appropriately or analysed as continuous variables) and who was applying the tests (experience and setting).

Validity

Construct validity and sensitivity to change:

- Time between measurements not too long
- Test order randomised
- Both tests conducted in each patient
- Two tests are conducted by the same raters, or raters randomised to tests and blinding of raters

Reliability

Inter-rater reliability:

- Randomisation of raters to patients (including order of raters)

- Blinding of raters results to results of other raters
- Not too long between tests
- Appropriate statistics – not correlation

Test-retest reliability and intra-rater reliability:

- The same measurement procedure
- The same observer and same measuring instrument
- Same environmental conditions
- Repetition over a short period of time

Internal consistency reliability:

- Same measurement procedure
- Same measuring instrument
- Same environmental conditions: (e.g. lighting) and same location
- Appropriate statistical analysis

4.3.9 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square p<0.1 or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

For diagnostic, prognostic studies and validity and reliability studies where no meta-analysis could be performed inconsistency in the results was assessed by comparing the tabulated results across studies and identifying any conflicting findings. These were discussed by the GDG and recorded in the LETR tables.

4.3.10 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

In this guideline, if the proportion with psoriatic arthritis was greater than 50% the evidence was considered to be indirect for the psoriasis population and would be downgraded.

4.3.111 Imprecision

The minimal important difference (MID) in the outcome between the two groups was the main criteria considered.

The thresholds of important benefits or harms, or the MID, for an outcome are important considerations for determining whether there is a "clinically important" difference between intervention and control groups and in assessing imprecision. For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, ether beneficial or harmful, and that would lead the patient or clinician to consider a change in the management".[31-34] An effect estimate larger than the MID is considered to be "clinically important".

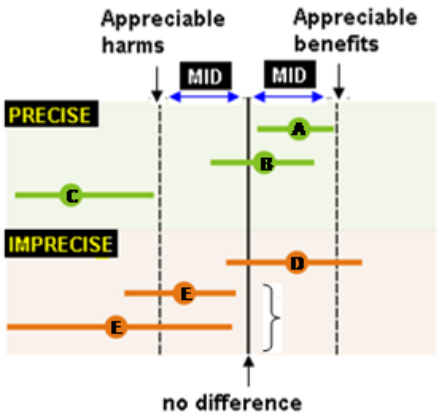
The difference between two interventions, as observed in the studies, was compared against the MID when considering whether the findings were of "clinical importance"; this is useful to guide decisions. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to strongly recommend one intervention over the other based on that outcome.

The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as illustrated in Figure 2 and outlined in Table 5. Essentially, if the confidence interval crossed the MID threshold and the line of no effect there was uncertainty in the effect estimate as the range of values encompassed by the confidence interval was consistent with two decisions and the effect estimate was rated as imprecise.

The thresholds for the MIDs were based on the default GRADEpro values of 0.25 either side of the line of no effect for dichotomous outcomes. For continuous outcomes the default MID was calculated by multiplying 0.5 by the standard deviation (taken as the median of the baseline standard deviations for all studies reporting this outcome or, if baseline values were not reported for all studies reporting this outcome, the median control group rate).

For the key outcomes the GDG discussed on a case-by-case basis whether the estimates were precise, and GRADE ratings were altered accordingly when the default MIDs were not deemed to be appropriate.

Figure 2: Illustration of precise and imprecision outcomes based on the confidence interval of outcomes in a forest plot



Position of confidence interval	Evidence statement
A	Statistically significant but not clinically important
B	It is unlikely that there is any difference
C	Statistically significant and clinically important
D	Uncertain whether there is any difference
E	Statistically significant difference of uncertain clinical importance

Source: Figure adapted from GRADEpro software

MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results.

Table 5: Criteria applied to determine precision for dichotomous and continuous outcomes

Precision estimate	Precision rating
The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect:	
• Does not cross either of the two minimal important difference (MID) thresholds (the threshold lines for appreciable benefit or harm); defined as precise.	'no serious imprecision'
• Crosses one of the two MID thresholds (appreciable benefit or appreciable harm) and the line of no effect; defined as imprecise.	'serious'
• Crosses both of the two MID thresholds (appreciable benefit and appreciable harm) and the line of no effect; defined as imprecise	'very serious'

For diagnostic reviews, the imprecision was based on the sensitivity, specificity PPV and NPV; however, if there was no majority in the assessment of imprecision across these statistics higher weighting was given to the outcomes deemed to be most important, for example in cases where it was most important to have a tests that are accurate for ruling out a diagnosis, the imprecision assessment would be based on sensitivity and NPV.

4.4 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

4.4.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual[29].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix I).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

4.4.111 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to had an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix H[29] and the health economics research protocol in Appendix C.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

4.4.112 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix H[29]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity[35].

Table 6: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*:

Item	Description
	• Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual, Appendix H[29]

Where economic studies compare multiple strategies, results are reported at the end of the relevant chapter in an alternative table summarising the study as a whole A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

4.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendices M, N and O for details of the health economic analyses undertaken for the guideline.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money [29,36].

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'[36].

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix H and Appendix I.
- Summary of clinical and economic evidence and quality (as presented in chapters 6-14).
- Forest plots (Appendix J).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix M, Appendix N and Appendix O).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were reached through discussions by the GDG. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the Linking Evidence to Recommendation Section in each section.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

4.5.2 Validation process

The guidance is subject to an eight week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

4.513 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.564 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

4.545 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

5 Guideline summary

5.1 Key priorities for implementation

From the full set of recommendations, the GDG selected 10 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual [29]. The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Assessment tool for disease severity and impact

- Assess people with all types of psoriasis for:
  - disease severity
  - the impact of disease on physical, psychological and social wellbeing
  - psoriatic arthritis
  - the presence of comorbidities.
- Following assessment in a non-specialist setting, offer referral for dermatology specialist advice if:
  - there is diagnostic uncertainty or
  - psoriasis is severe or extensive, for example more than 10% of BSA involvement or
  - psoriasis cannot be controlled with topical therapy or
  - acute guttate psoriasis requires phototherapy or
  - nail disease has a major functional or cosmetic impact or
  - any type of psoriasis is having a major impact on a person's physical, psychological or social wellbeing).

Assessment and referral for psoriatic arthritis

- As soon as psoriatic arthritis is suspected, refer the person to a rheumatologist for assessment and advice about planning their care.

Identification of comorbidities

- Discuss risk factors for comorbidities with people who have psoriasis of all severities. Explain that they are at higher risk of hypertension, diabetes, obesity and hyperlipidaemia than people without psoriasis. Offer preventative advice and healthy lifestyle information in line with the following NICE guidance:
  - 'Lipid modification' (NICE clinical guideline 67)
  - 'Obesity' (NICE clinical guideline 43)
  - 'Preventing type 2 diabetes: population and community-level interventions in high-risk groups and the general population' (NICE public health guidance 35)
  - 'Prevention of cardiovascular disease at population level' (NICE public health guidance 25)
  - 'Alcohol-use disorders: preventing the development of hazardous and harmful drinking' (NICE public health guidance 24)
  - 'Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities' (NICE public health guidance 10).

Topical therapy: general recommendations

- Offer practical support and advice about the use and application of topical treatments. Advice should be provided by healthcare professionals who are trained and competent in the use of

topical therapies. Support people to adhere to treatment in line with 'Medicines adherence' (NICE clinical guideline 76).

Phototherapy

- Offer narrowband ultraviolet B (UVB) phototherapy to people with plaque or guttate-pattern psoriasis that cannot be controlled with topical treatments alone. Treatment with narrowband UVB phototherapy can be given three or two times a week depending on patient preference. Tell people receiving narrowband UVB that a response may be achieved more quickly with treatment three times a week. Offer other second or third line treatment options when:
  - narrowband UVB phototherapy results in an inadequate response or is poorly tolerated **or**
  - there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) **or**
  - accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) **or**
  - the person is at especially high risk of skin cancer.
- Healthcare professionals who are giving phototherapy should be trained and competent in its use and should ensure an appropriate clinical governance framework is in place to promote adherence to the indications for and contraindications to treatment, dosimetry and national policy on safety standards for phototherapy.

Systemic therapy

- Be aware of the benefits of, contraindications to and adverse effects associated with systemic treatments. Explain the risks and benefits to people undergoing this treatment using absolute risks and natural frequencies when possible. Support and advice should be provided by healthcare professionals who are trained and competent in the use of systemic therapies.

Choice of drugs (systemic non-biological therapy)

- Offer systemic therapy to people with psoriasis if:
  - it cannot be controlled with topical therapy **and**
  - it has a significant impact on physical, psychological or social wellbeing **and**
  - one or more of the following apply:
  - psoriasis is extensive (for example, BSA of more than 10% affected or a PASI score of more than 10) **or**
  - psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) **or**
  - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

Systemic biological therapy

- Consider changing to an alternative biological drug in adults with psoriasis in whom there is an inadequate response to a first biological drug (either following the first 3 months of treatment [primary failure], or following an initially adequate response [secondary failure]), or if the first biological drug cannot be tolerated or becomes contraindicated.

5.2 Full list of recommendations

None of the interventions, with the exception of topical calcipotriol, are licensed for use in psoriasis in children and there is little or no evidence in children. Healthcare professionals should refer to the individual Summary of Product Characteristics (SPCs) and the British National Formulary (BNF) for children before prescribing and informed consent should be obtained and documented.

1. Offer people with all types of psoriasis support and information tailored to suit their individual needs and circumstances, in a range of different formats so they can confidently understand:
   - their diagnosis and treatment options
   - lifestyle risk factors that are relevant
   - how to recognise a flare
   - how to use prescribed treatments safely and effectively (for example, how to apply topical treatments and how to minimise the risk of side effects through safe monitoring of medicines)
   - when and how to seek further general or specialist review
   - strategies to deal with the impact of psoriasis on physical, psychological and social wellbeing.
2. When offering treatments to a person with any type of psoriasis:
   - ensure the treatment strategy is developed to meet the individual's health goals so that the impact of their condition is minimised and use relevant assessment tools to ensure these goals are met
   - take into account the age and individual circumstances of the person, disease phenotype, severity and impact, co-existing psoriatic arthritis, comorbidities and previous treatment history
   - discuss the risks and benefits of treatment options with the person and where possible include use of absolute risk and natural frequency.
3. Assess whether support and information needs updating or revising at every review or interaction with the person affected, in partucular during transition from children's services to adult services, when new interventions become available, and when the person's disease severity or circumstances change.
4. Provide a single point of contact to help people with all types of psoriasis access appropriate information and advice about their condition and the services available at each stage of the care pathway.
5. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138). Recommendations on shared decision making, including discussions about investigation or treatment options and risks and benefits can be found in section 1.5 of that guideline.
6. Assess people with all types of psoriasis for:
   - disease severity
   - the impact of disease on physical, psychological and social wellbeing
   - psoriatic arthritis
   - the presence of comorbidities.
7. Assess psoriasis severity and impact:
   - at first presentation
   - before referral for specialist advice and at any referral point in the treatment pathway
   - to evaluate the efficacy of interventions.
8. When assessing the disease severity, record:
   - the results of a Static Physician's Global Assessment (PGA) (classified as clear, nearly clear, mild, moderate, severe or very severe)
   - the body surface area (BSA) affected

- any involvement of nails and high-impact or difficult-to-treat sites (for example, the face, scalp, palms, soles, flexures and genitals)
- any systemic upset (for example, in people with erythroderma or generalised pustular psoriasis).

9. In specialist settings, use a validated tool to assess severity, for example the Psoriasis Activity and Severity Index (PASI) in adults and for young children use the PGA. Be aware that:
   - PASI and BSA are not validated for use in children
   - erythema may be underestimated in people with darker skin types, such as skin types V and VI on the Fitzpatrick scale.

10. Assess the impact of all types of psoriasis on physical, psychological and social wellbeing by asking:
    - what aspects of their daily living are affected by the person's psoriasis
    - how the person is coping with their skin condition and any treatments they are using, and if they need further advice or support
    - if their psoriasis has a big impact on their mood.

In children and young people also ask about impact on the family and ask age-appropriate questions.

11. In specialist settings and if practical in non-specialist settings, use a validated tool to assess the impact of any type of psoriasis on physical, psychological and social wellbeing, for example the:
    - Dermatology Life Quality Index (DLQI) for adults **or**
    - Children's Dermatology Life Quality Index (CDLQI) for children and young people.

12. Assess whether people with any type of psoriasis are depressed when assessing disease severity and impact, and when escalating therapy. If appropriate offer information, advice and support in line with 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91) for adults and 'Depression in children and young people' (NICE clinical guideline 28) for children and young people.

13. Use the Nail Psoriasis Severity Index to assess nail disease in specialist settings:
    - if there is a major functional or cosmetic impact **or**
    - before and after treatment is initiated specifically for nail disease.

14. Following assessment in a non-specialist setting, offer referral for dermatology specialist advice if:
    - there is diagnostic uncertainty **or**
    - psoriasis is severe or extensive, for example more than 10% of BSA involvement **or**
    - psoriasis cannot be controlled with topical therapy **or**
    - acute guttate psoriasis requires phototherapy **or**
    - nail disease has a major functional or cosmetic impact **or**
    - any type of psoriasis is having a major impact on a person's physical, psychological or social wellbeing.

15. People with unstable psoriasis, for example generalised pustular psoriasis or erythroderma, should be referred immediately for same-day specialist assessment and treatment.

16. When using an assessment tool for a person with any type of psoriasis take account their age, any disabilities (such as physical, visual or cognitive impairment), and any language or other communication difficulties, and provide help and support if needed. Ensure that the chosen assessment tool continues to be a sufficiently accurate measure.

17. Offer specialist referral to children with psoriasis at presentation.

18. Offer annual assessment for psoriatic arthritis to people with any type of psoriasis. Assessment is especially important within the first 10 years of onset of psoriasis.

19. Use a validated tool to assess adults for psoriatic arthritis in primary care and specialist settings, for example the Psoriasis Epidemiological Screening Tool (PEST). Be aware that the PEST does not detect axial arthritis or inflammatory back pain.

20. As soon as psoriatic arthritis is suspected, refer the person to a rheumatologist for assessment and advice about planning their care.

21. Offer a cardiovascular risk assessment using a validated risk estimation tool to adults with severe psoriasis at presentation, and offer further assessments every 5 years, or more frequently if indicated following risk assessment. For further information see 'Lipid modification' (NICE clinical guideline 67).

22. Discuss risk factors for comorbidities with people who have psoriasis of all severities. Explain that they are at higher risk of hypertension, diabetes, obesity and hyperlipidaemia than people without psoriasis. Offer preventative advice and healthy lifestyle information in line with the following NICE guidance:
    - 'Lipid modification' (NICE clinical guideline 67)
    - 'Obesity' (NICE clinical guideline 43)
    - 'Preventing type 2 diabetes: population and community-level interventions in high-risk groups and the general population' (NICE public health guidance 35)
    - 'Prevention of cardiovascular disease at population level' (NICE public health guidance 25)
    - 'Alcohol-use disorders: preventing the development of hazardous and harmful drinking' (NICE public health guidance 24)
    - 'Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities' (NICE public health guidance 10).

23. For people with multiple comorbidities and any type of psoriasis needing second- or third-line therapy ensure multidisciplinary working and communication between specialties and, if needed, interdisciplinary team working (for example when both skin and joints are significantly affected).

24. Be aware that psoriasis is a risk factor for venous thromboembolism, especially in people with severe psoriasis and:
    - explain this risk to people with psoriasis
    - offer advice on how to minimise the risk (for example, during hospital admission, surgery or periods of immobility)
    - manage the risk in line with 'Venous thromboembolism: reducing the risk' (NICE clinical guideline 92).

25. Offer people with psoriasis topical therapy as first-line treatment and escalate to second-line treatment (that is, phototherapy or systemic non-biological therapy) or third-line treatment (systemic biological therapy) if psoriasis is extensive and/or severe.

26. Offer practical support and advice about the use and application of topical treatments. Advice should be provided by healthcare professionals who are trained and competent in the use of topical therapies. Support people to adhere to treatment in line with 'Medicines adherence' (NICE clinical guideline 76).

27. Be aware that continuous use of potent or very potent corticosteroids may cause:
    - irreversible skin atrophy and striae
    - psoriasis to become unstable
    - systemic side effects when applied continuously to extensive psoriasis.

Explain the risks of these side effects to people undergoing treatment and discuss how to avoid them.

28. When offering a corticosteroid for topical treatment choose a low-cost preparation.

29. Do not use potent or very potent corticosteroids on the face or flexures, including genital sites.

30. Do not use very potent corticosteroids continuously at any site for longer than 4 weeks.

31. Do not use potent corticosteroids continuously at any site for longer than 8 weeks.

32. When offering topical agents take into account patient preference, cosmetic acceptability, practical aspects of application and the site(s) and extent of psoriasis to be treated. Discuss the variety of formulations available and use:
    - cream or lotion for widespread psoriasis
    - lotion, solution or gel for the scalp or hair-bearing areas
    - ointment to treat areas with thick adherent scale.

Be aware that topical treatment alone may not provide satisfactory disease control, especially in people with severe psoriasis.

33. If a person with psoriasis has a physical disability or visual impairment and needs topical therapy, offer advice and practical support that take into account the person's individual needs.

34. Arrange a review appointment at 4 weeks after starting a new topical treatment strategy to evaluate tolerability, toxicity and initial response to treatment.

35. Discuss with people whose psoriasis is responding to topical treatment:
    - the importance of continuing treatment until a satisfactory outcome is achieved (for example clear or nearly clear) or up to the recommended maximum treatment period for corticosteroids (see sections 8.5 and 8.12)
    - that relapse occurs in most people after treatment is stopped
    - that topical treatments can be used as and when required to maintain satisfactory disease control.

36. Offer people with psoriasis a supply of their topical treatment to keep at home for the self-management of their condition.

37. In people whose psoriasis has not responded satisfactorily to a topical treatment strategy, before changing to an alternative treatment:
    - discuss with the person whether they have any difficulties with application, cosmetic acceptability or tolerability and where relevant offer an alternative formulation
    - consider other possible reasons for non-adherence in line with 'Medicines adherence' (NICE clinical guideline 76).

38. Offer a potent corticosteroid applied once daily plus vitamin D or a vitamin D analogue applied once daily (applied separately, for example one agent applied in the morning and the other in the evening) for a maximum period of 8 weeks as initial treatment for psoriasis of the trunk or limbs in adults.

39. If once-daily application of a potent corticosteroid plus vitamin D or a vitamin D analogue does not result in clearance, near clearance or satisfactory control of psoriasis of the trunk or limbs in adults after 8 weeks, offer vitamin D or a vitamin D analogue alone applied twice daily.

40. If twice-daily application of vitamin D or a vitamin D analogue does not result in clearance, near clearance or satisfactory control of trunk or limb psoriasis in adults by 8–12 weeks offer either:
    - a potent corticosteroid applied twice daily for up to 8 weeks **or**
    - a coal tar preparation applied once or twice daily.

41. If a twice-daily potent corticosteroid or coal tar preparation cannot be used and a once-daily preparation would improve adherence, offer a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily for up to 8 weeks.

42. Offer treatment with very potent corticosteroids in adults with trunk or limb psoriasis only:
    - in specialist settings under careful supervision
    - when other topical treatment strategies have failed
    - for a maximum period of 4 weeks.

43. Consider short-contact dithranol for treatment-resistant psoriasis of the trunk or limbs and either:
    - give educational support for self-use **or**
    - ensure treatment is given in a day-care setting.

44. Offer a review at least annually to people with trunk or limb psoriasis who are using a potent or very potent corticosteroid (either as monotherapy or in combined preparations) to assess for the presence of steroid atrophy and other adverse effects.

45. For children and young people with trunk or limb psoriasis consider either:
    - calcipotriol applied once daily **or**
    - a potent corticosteroid applied once daily.

Review treatment 2 weeks after starting treatment.

46. Offer a potent corticosteroid applied once daily for a maximum period of 8 weeks as initial treatment for people with scalp psoriasis. Choose a low-cost preparation.

47. Show people with scalp psoriasis how to safely apply corticosteroid topical treatment.

48. If treatment with a potent corticosteroid does not result in clearance, near clearance or satisfactory control of scalp psoriasis after 4 weeks consider:
    - a different formulation of the potent corticosteroid (for example, a shampoo or mousse) **and/or**
    - topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before further application of the potent corticosteroid.

If the response remains unsatisfactory after a further 4 weeks of treatment offer:
    - a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily for up to 8 weeks **or**
    - vitamin D or a vitamin D analogue applied once daily.

49. If continuous treatment with either a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily or vitamin D or a vitamin D analogue applied daily for up to 8 weeks does not result in clearance, near clearance aor satisfactory control of scalp psoriasis offer:

- a very potent corticosteroid applied up to twice daily for 2 weeks (up to a maximum of 4 weeks) for adults only **or**
- coal tar applied once or twice daily **or**
- referral to a specialist for additional support with topical applications and/or advice on alternative treatment options.

50. Consider topical vitamin D or a vitamin D analogue alone for the treatment of scalp psoriasis only in people who:
    - are intolerant to or cannot use topical corticosteroids at this site **or**
    - have mild-to-moderate scalp psoriasis.
51. Do not offer coal tar-based shampoos alone for the treatment of plaque-type scalp psoriasis.
52. Do not use very potent corticosteroids for scalp psoriasis in children.
53. Offer a short-term mild or moderate potency corticosteroid applied once or twice daily (for a maximum of 2 weeks) to people with psoriasis of the face, flexures or genitals.
54. Be aware that the face, flexures and genitals are particularly vulnerable to steroid atrophy and that corticosteroids should only be used for short-term treatment of psoriasis (1–2 weeks per month). Explain the risks to people undergoing this treatment and how to minimise them
55. For people with psoriasis of the face, flexures or genitals who show an unsatisfactory response to, or require ongoing continuous treatment with, short-term moderate potency corticosteroids to maintain control, offer a calcineurin inhibitor applied twice daily for 4 weeks. Calcineurin inhibitors should be initiated by healthcare professionals with expertise in treating psoriasis.
56. Do not use very potent corticosteroids in children.
57. When prescribing topical agents at facial, flexural and genital sites take into account that they may cause irritation, and inform people undergoing treatment of these risks and how to minimise them.
58. Offer narrowband ultraviolet B (UVB) phototherapy to people with plaque or guttate-pattern psoriasis that cannot be controlled with topical treatments alone. Treatment with narrowband UVB phototherapy can be given three or two times a week depending on patient preference. Tell people receiving narrowband UVB that a response may be achieved more quickly with treatment three times a week.
59. Offer other second or third line treatment options when:
    - narrowband UVB phototherapy results in an inadequate response or is poorly tolerated **or**
    - there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) **or**
    - accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) **or**
    - the person is at especially high risk of skin cancer.
60. Consider psoralen (oral or topical) with local ultraviolet A (UVA) irradiation to treat palmoplantar pustulosis.
61. Do not routinely use phototherapy (narrowband UVB, broadband UVB or psoralen plus ultraviolet A [PUVA]) as maintenance therapy.

62. Ensure that all phototherapy equipment is safety-checked and maintained in line with local and national policy.

63. Healthcare professionals who are giving phototherapy should be trained and competent in its use and should ensure an appropriate clinical governance framework is in place to promote adherence to the indications for and contraindications to treatment, dosimetry and national policy on safety standards for phototherapy.

64. Do not routinely offer co-therapy with acitretin when administering PUVA.

65. Consider topical adjunctive therapy in people receiving phototherapy with broadband or narrowband UVB who:
    - have plaques at sites that are resistant or show an inadequate response (for example, the lower leg) to phototherapy alone, or at difficult-to-treat or high-need, covered sites (for example, flexures and the scalp)
    - do not wish to take systemic drugs or in whom systemic drugs are contraindicated.

66. Do not use PUVA in people with psoriasis and a genetic predisposition to skin cancer for example, xeroderma pigmentosum or familial melanoma.

67. Do not use PUVA when other appropriate treatments are available in:
    - people with a personal history of skin cancer **or**
    - people who have already received 150 PUVA treatments **or**
    - children.

68. Use PUVA with caution and consider other treatment options in:
    - people at risk of skin cancer (melanoma and non-melanoma type) (see 'Improving outcomes for people with skin tumours including melanoma' [NICE cancer service guidance])
    - people with lighter skin types, such as skin types I or II on the Fitzpatrick scale
    - people who are likely to require ciclosporin or long-term methotrexate
    - young people.

69. When considering PUVA for psoriasis (plaque or localised palmoplantar pustulosis) discuss with the person:
    - other treatment options
    - that any exposure is associated with an increased risk of skin cancer (squamous cell carcinoma)
    - that subsequent use of ciclosporin may increase the risk of skin cancer, particularly if they have already received more than 150 PUVA treatments
    - that risk of skin cancer is related to the number of UV exposures.

70. Offer lifetime skin cancer surveillance to people treated with PUVA who have:
    - had more than 150 PUVA treatments **or**
    - developed skin cancer.

71. Document (for example, in a national record) the cumulative number of UV exposures.

72. Only use systemic therapy in specialist settings.

73. When offering systemic therapy, tailor the choice of agent and dosing schedule to the needs of the individual and include consideration of:
    - the person's age

- disease phenotype, pattern of activity and previous treatment history
- disease severity and impact
- the presence of psoriatic arthritis (in consultation with a rheumatologist)
- conception plans
- comorbidities
- the person's views.

74. Be aware of the benefits of, contraindications to and adverse effects associated with systemic treatments. Explain the risks and benefits to people undergoing this treatment using absolute risks and natural frequencies when possible. Support and advice should be provided by healthcare professionals who are trained and competent in the use of systemic therapies.

75. Monitor people using systemic treatment for all types of psoriasis in accordance with national and local drug guidelines and policy. Take appropriate action in the event of laboratory abnormalities or adverse events.

76. Offer adjunctive topical therapy to optimise treatment outcomes.

77. Offer people with psoriasis who are starting treatment with a systemic non-biological or biological drug the opportunity to participate in long-term safety registries (for example the British Association of Dermatologists Biologic Interventions Register).

78. Offer systemic therapy to people with psoriasis if:

- it cannot be controlled with topical therapy **and**
- it has a significant impact on physical, psychological or social wellbeing **and**
- one or more of the following apply:
  - psoriasis is extensive (for example, BSA of more than 10% affected or a PASI score of more than 10) **or**
  - psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) **or**
  - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

79. In people with both active psoriatic arthritis and psoriasis that fulfils the criteria for systemic therapy (see recommendation 78) consider the choice of systemic agent in consultation with a rheumatologist. For further information see 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal guidance 199).

80. Offer methotrexate as the first choice of systemic agent for people with psoriasis that fulfils the criteria for systemic therapy (see recommendation 78) except in the circumstances described in recommendations 81 and 82.

81. When considering the risks and benefits of treating any type of psoriasis with methotrexate, be aware that methotrexate can cause a clinically significant rise in transaminases and that long-term therapy may be associated with liver fibrosis (see recommendations 91 to 95).

82. Offer ciclosporin as the first choice of systemic agent for people with psoriasis that fulfils the criteria for systemic therapy (see recommendation 78) and who:

- need rapid or short-term disease control (for example a psoriasis flare) **or**
- have palmoplantar pustulosis **or**
- are considering conception (both men and women) and systemic therapy cannot be avoided.

83. Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate.

84. Consider acitretin for adults, and in exceptional cases only for children, in the following circumstances:
    - if methotrexate and ciclosporin are not appropriate or have failed **or**
    - for people with pustular forms of psoriasis.

85. Use incremental dosing of methotrexate (for example, starting with an initial dose of 5–10 mg once a week) in adults and gradually increase the dose up to the target dose of 25 mg a week. Assess the treatment response after 3 months at the target dose of methotrexate and stop treatment if the response is inadequate (for example, a decrease of less than 75% in PASI score or a decrease of less than 50% in PASI score and 5 points in DLQI score).

86. Use the lowest possible therapeutic dose of methotrexate to maintain remission.

87. Use 2.5–3 mg/kg a day of ciclosporin for adults and children. Escalate to 5 mg/kg a day after 4 weeks only when there is no response to the lower dose or when rapid disease control is necessary (for example in severe unstable disease). Assess the treatment response after 3 months at the optimum dose of ciclosporin and stop treatment if the response is inadequate (for example, less than a 75% decrease in PASI score or less than a 50% decrease in PASI score and less than 5 points in DLQI score).

88. Use the lowest possible therapeutic dose of ciclosporin to maintain remission for up to 1 year. Consider other treatment options when disease relapses rapidly on stopping ciclosporin therapy (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months of stopping treatment). Do not use ciclosporin continuously for more than 1 year unless disease is severe or unstable and other treatment options cannot be used.

89. Use incremental dosing of acitretin to minimise mucocutaneous side effects and achieve a target dose of 25 mg daily in adults. Consider dose escalation to a maximum of 50 mg daily when no other treatment options are available.

90. When reviewing response to systemic therapy, take into account:
    - disease severity compared with baseline (for example, PASI baseline to endpoint score)
    - control of psoriatic arthritis disease activity (in consultation with a rheumatologist if necessary)
    - the impact of the disease on the person's physical, psychological and social wellbeing
    - the benefits versus the risks of continued treatment
    - the views of the person and, in children, their family.

91. Before and during methotrexate treatment, evaluate for potential hepatotoxicity.

92. Use standard liver function tests and serial serum procollagen III levels to monitor for abnormalities during treatment with methotrexate, taking into account pre-existing risk factors (for example obesity, diabetes and alcohol use), baseline results and trends over time.

93. When using serum procollagen III levels to exclude liver fibrosis or cirrhosis, be aware that the:
    - test cannot be used in children
    - results may be unreliable in people with psoriatic arthritis
    - positive predictive value is 23–95% and the negative predictive value is 89–100%.

94. Provide advice on modifiable risk factors for liver disease prior to and during therapy including alcohol intake and weight reduction if appropriate. For more information see 'Alcohol-use

disorders: physical complications' (NICE clinical guideline 100), 'Alcohol-use disorders: preventing the development of hazardous and harmful drinking' (NICE public health guidance 24) and 'Obesity' (NICE clinical guideline 43).

95. Seek timely specialist advice and consider referral to a clinician with expertise in liver disease if the results of liver tests are abnormal.

96. Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met.

- The disease is severe as defined by a total PASI of 10 or more and aDLQI of more than 10.
- The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant of, or has a contraindication to, these treatments.

97. Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:

- a 75% reduction in the PASI score (PASI 75) from when treatment started **or**
- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.

98. When using the DLQI, healthcare professionals should ensure that when reaching conclusions on the severity of plaque psoriasis they take into account a person's disabilities (such as physical impairments) and linguistic or other communication difficulties. In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of adalimumab in accordance with recommendation 97.

99. Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.

- The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10.
- The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments.

100. Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:

- a 75% reduction in the PASI score from when treatment started (PASI 75) **or**
- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.

101. It is recommended that the use of etanercept for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

102. Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.

- The disease is very severe as defined by a total PASI of 20 or more and a DLQI of more than 18.

- The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments.

103. Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:

- a 75% reduction in the PASI score from when treatment started (PASI 75) **or**
- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.

104. When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with recommendation 103.

105. Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met.

- The disease is severe, as defined by a total PASI score of 10 or more and a DLQI score of more than 10.
- The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA, or the person is intolerant of or has a contraindication to these treatments.
- The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.

106. Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:

- a 75% reduction in the PASI score (PASI 75) from when treatment started **or**
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started.

107. When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.

108. Consider changing to an alternative biological drug in adults with psoriasis in whom there is an inadequate response to a first biological drug (either following the first 3 months of treatment [primary failure], or following an initially adequate response [secondary failure]), or if the first biological drug cannot be tolerated or becomes contraindicated.

109. For adults in whom there is an inadequate response to a second biological drug, seek supra-specialist advice from a clinician with expertise in biological therapy.

110. If a person has both psoriasis and psoriatic arthritis, take into account both conditions before making changes to biological therapy and manage their treatment in consultation with a rheumatologist. For further information see ‘Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis’ (NICE technology appraisal guidance 199).

5.3 Key research recommendations

What validated tools can be used in people (including children) to assess disease severity and impact in non-specialist and specialist healthcare settings to facilitate assessment, appropriate referral, treatment planning and measurement of outcomes?

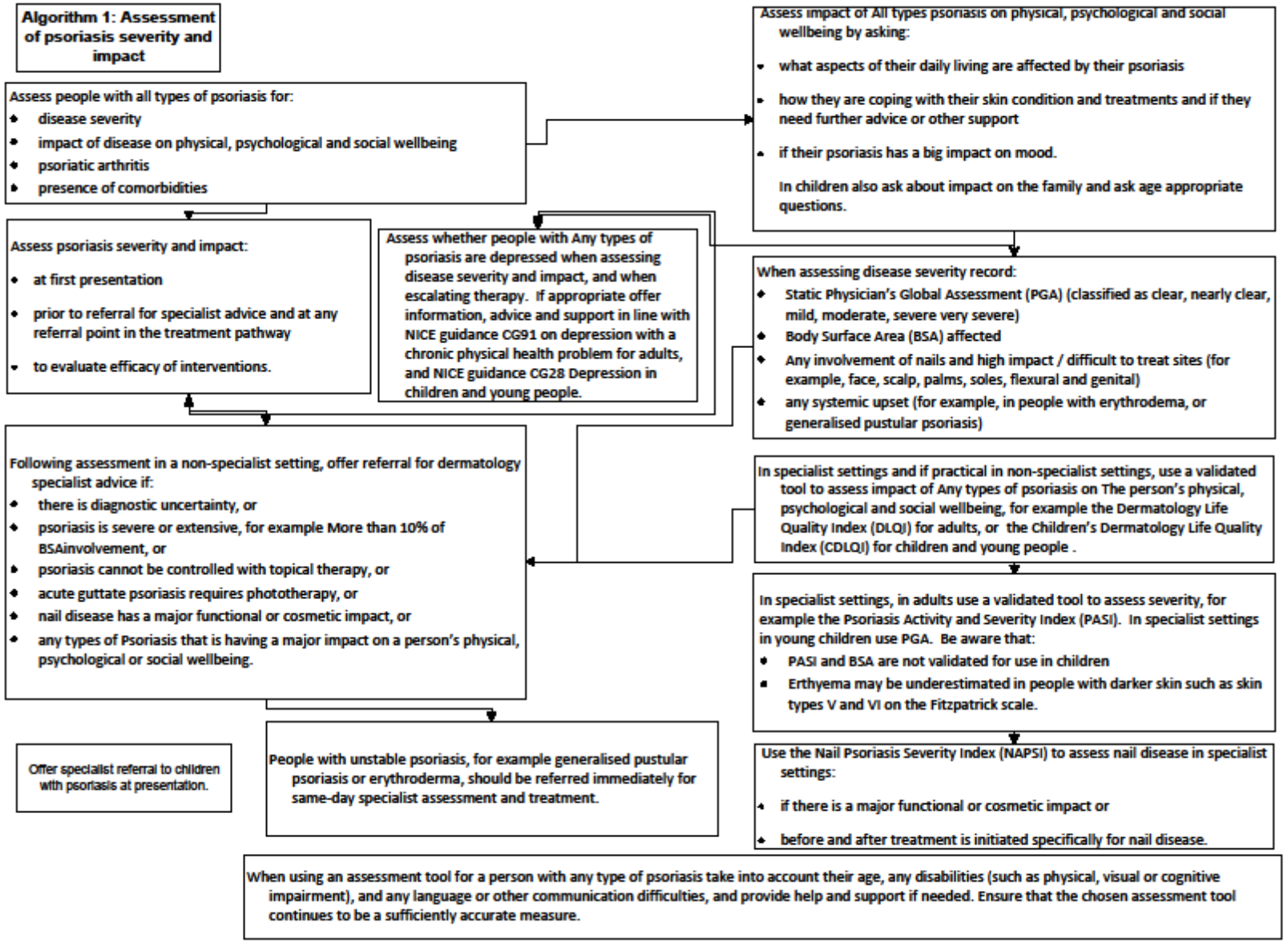
Does treating psoriasis modify the risk of cardiovascular disease and are there any clinical (for example, demographic, phenotypic) or laboratory (for example genetic or immune markers) that identify those most likely to benefit?

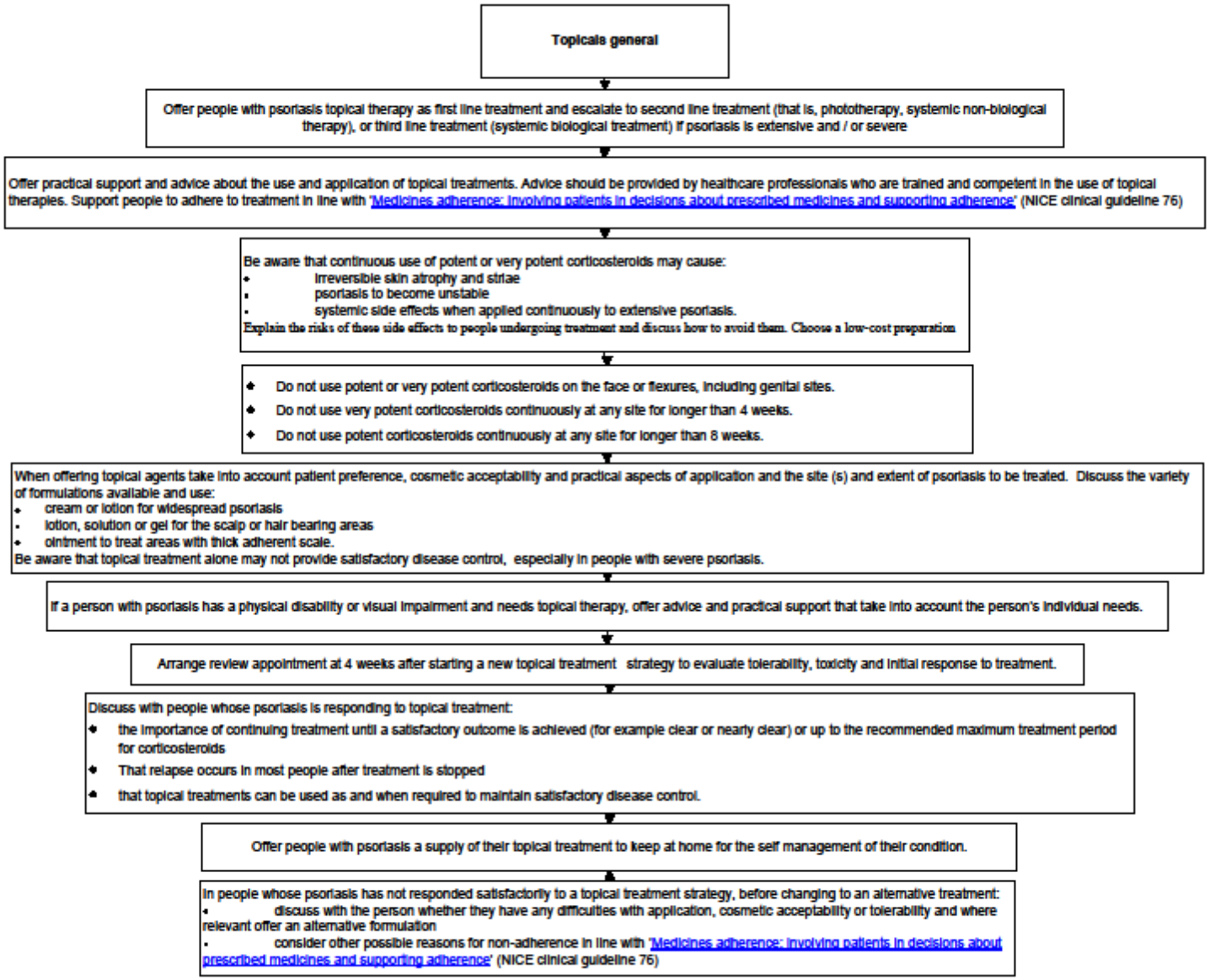
What is the impact of methotrexate compared with other approaches to care (for example, other systemic or biologic therapies) on risk of significant liver disease in people with psoriasis and do risk factors such as obesity, alcohol or diabetes alter this risk?

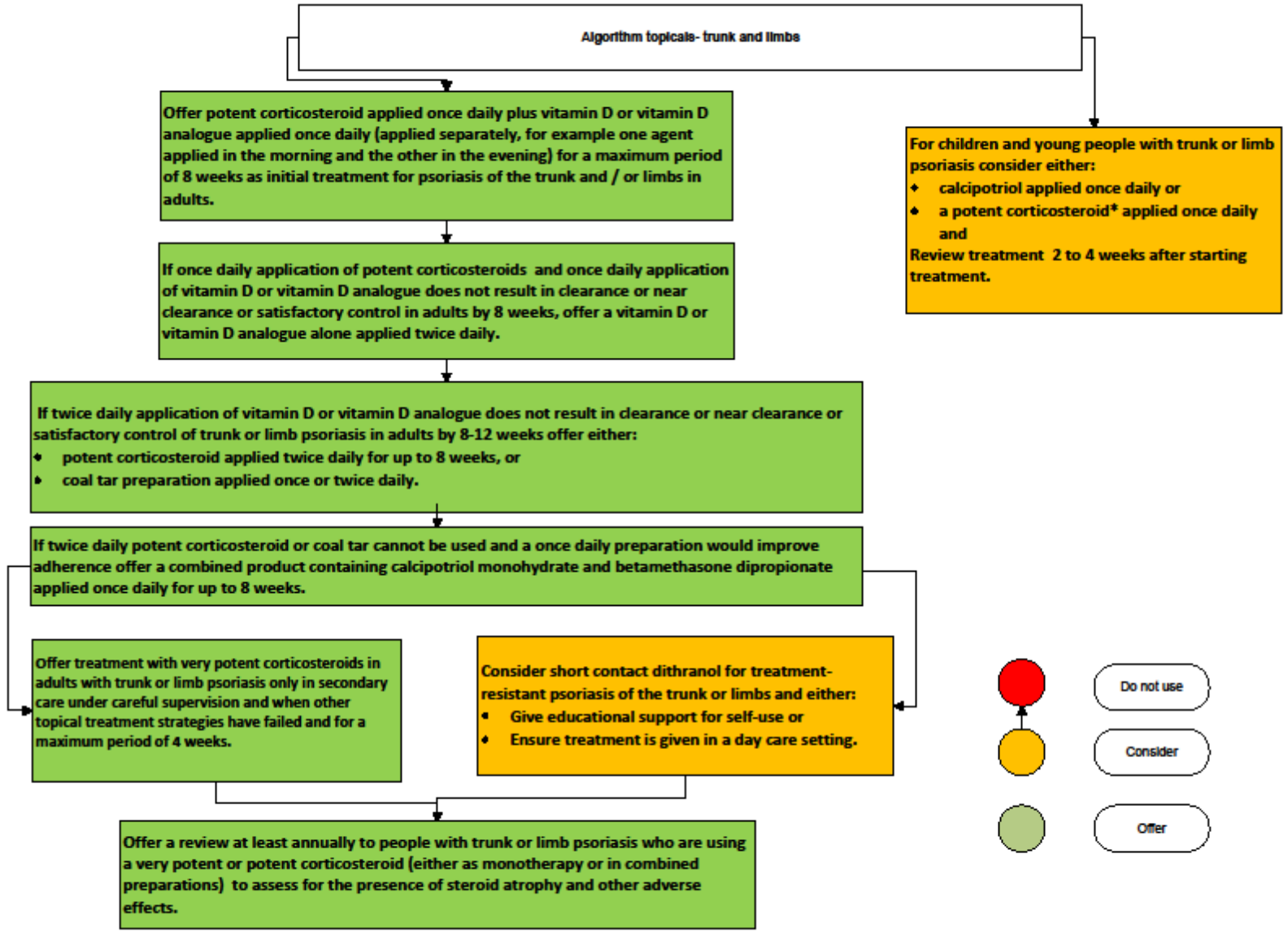
In people with psoriasis, does early intervention to achieve and maintain complete disease remission alter the long term prognosis in terms of psoriasis severity , co-morbidities (including psoriatic arthritis), or treatment related adverse effects and are there any clinical (for example, demographic, phenotypic) or laboratory (for example genetic or immune markers) that can be used to identify those most likely to benefit from this treatment approach?

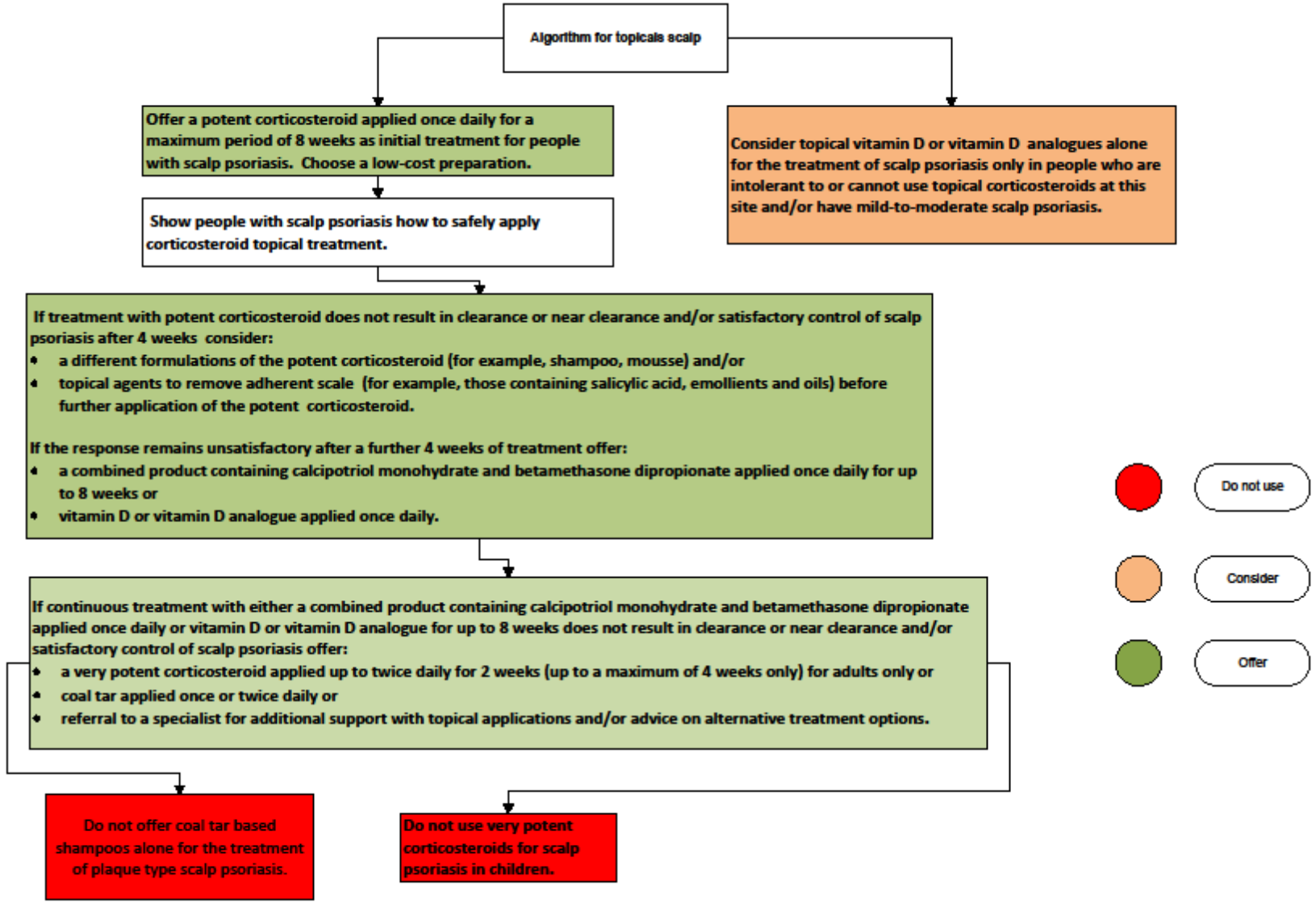
Do structured psoriasis focussed educational programmes improve patient confidence, well-being and disease control as compared to standard care?

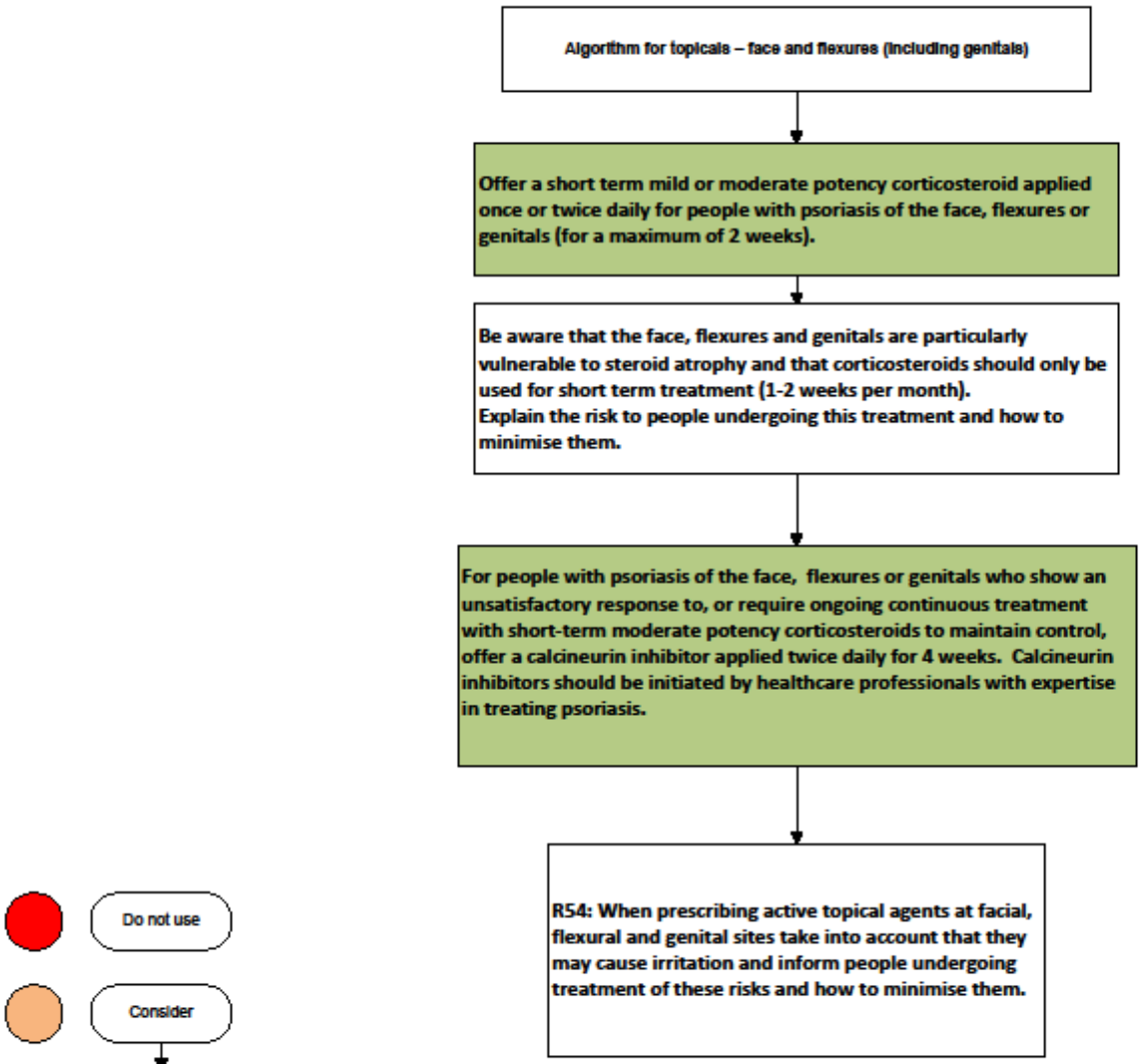
5.4 Algorithms


Algorithm 1: Assessment of psoriasis severity and impact
Assess people with all types of psoriasis for:
disease severity
impact of disease on physical, psychological and social wellbeing
psoriatic arthritis
presence of comorbidities
Assess impact of All types psoriasis on physical, psychological and social wellbeing by asking:
what aspects of their daily living are affected by their psoriasis
how they are coping with their skin condition and treatments and if they need further advice or other support
if their psoriasis has a big impact on mood.
In children also ask about impact on the family and ask age appropriate questions.
Assess psoriasis severity and impact:
at first presentation
prior to referral for specialist advice and at any referral point in the treatment pathway
to evaluate efficacy of interventions.
Assess whether people with Any types of psoriasis are depressed when assessing disease severity and impact, and when escalating therapy. If appropriate offer information, advice and support in line with NICE guidance CG91 on depression with a chronic physical health problem for adults, and NICE guidance CG28 Depression in children and young people.
When assessing disease severity record:
Static Physician's Global Assessment (PGA) (classified as clear, nearly clear, mild, moderate, severe very severe)
Body Surface Area (BSA) affected
Any involvement of nails and high impact / difficult to treat sites (for example, face, scalp, palms, soles, flexural and genital)
any systemic upset (for example, in people with erythrodema, or generalised pustular psoriasis)
Following assessment in a non-specialist setting, offer referral for dermatology specialist advice if:
there is diagnostic uncertainty, or
psoriasis is severe or extensive, for example More than 10% of BSAinvolvement, or
psoriasis cannot be controlled with topical therapy, or
acute guttate psoriasis requires phototherapy, or
nail disease has a major functional or cosmetic impact, or
any types of Psoriasis that is having a major impact on a person's physical, psychological or social wellbeing.
In specialist settings and if practical in non-specialist settings, use a validated tool to assess impact of Any types of psoriasis on The person's physical, psychological and social wellbeing, for example the Dermatology Life Quality Index (DLQI) for adults, or the Children's Dermatology Life Quality Index (CDLQI) for children and young people .
In specialist settings, in adults use a validated tool to assess severity, for example the Psoriasis Activity and Severity Index (PASI). In specialist settings in young children use PGA. Be aware that:
PASI and BSA are not validated for use in children
Erthyema may be underestimated in people with darker skin such as skin types V and VI on the Fitzpatrick scale.
Use the Nail Psoriasis Severity Index (NAPSI) to assess nail disease in specialist settings:
if there is a major functional or cosmetic impact or
before and after treatment is initiated specifically for nail disease.
Offer specialist referral to children with psoriasis at presentation.
People with unstable psoriasis, for example generalised pustular psoriasis or erythroderma, should be referred immediately for same-day specialist assessment and treatment.
When using an assessment tool for a person with any type of psoriasis take into account their age, any disabilities (such as physical, visual or cognitive impairment), and any language or other communication difficulties, and provide help and support if needed. Ensure that the chosen assessment tool continues to be a sufficiently accurate measure.


Topicals general
Offer people with psoriasis topical therapy as first line treatment and escalate to second line treatment (that is, phototherapy, systemic non-biological therapy), or third line treatment (systemic biological treatment) if psoriasis is extensive and / or severe
Offer practical support and advice about the use and application of topical treatments. Advice should be provided by healthcare professionals who are trained and competent in the use of topical therapies. Support people to adhere to treatment in line with 'Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence' (NICE clinical guideline 76)
Be aware that continuous use of potent or very potent corticosteroids may cause:
irreversible skin atrophy and striae
psoriasis to become unstable
systemic side effects when applied continuously to extensive psoriasis.
Explain the risks of these side effects to people undergoing treatment and discuss how to avoid them. Choose a low-cost preparation
Do not use potent or very potent corticosteroids on the face or flexures, including genital sites.
Do not use very potent corticosteroids continuously at any site for longer than 4 weeks.
Do not use potent corticosteroids continuously at any site for longer than 8 weeks.
When offering topical agents take into account patient preference, cosmetic acceptability and practical aspects of application and the site (s) and extent of psoriasis to be treated. Discuss the variety of formulations available and use:
cream or lotion for widespread psoriasis
lotion, solution or gel for the scalp or hair bearing areas
ointment to treat areas with thick adherent scale.
Be aware that topical treatment alone may not provide satisfactory disease control, especially in people with severe psoriasis.
If a person with psoriasis has a physical disability or visual impairment and needs topical therapy, offer advice and practical support that take into account the person's individual needs.
Arrange review appointment at 4 weeks after starting a new topical treatment strategy to evaluate tolerability, toxicity and initial response to treatment.
Discuss with people whose psoriasis is responding to topical treatment:
the importance of continuing treatment until a satisfactory outcome is achieved (for example clear or nearly clear) or up to the recommended maximum treatment period for corticosteroids
That relapse occurs in most people after treatment is stopped
that topical treatments can be used as and when required to maintain satisfactory disease control.
Offer people with psoriasis a supply of their topical treatment to keep at home for the self management of their condition.
In people whose psoriasis has not responded satisfactorily to a topical treatment strategy, before changing to an alternative treatment:
discuss with the person whether they have any difficulties with application, cosmetic acceptability or tolerability and where relevant offer an alternative formulation
consider other possible reasons for non-adherence in line with 'Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence' (NICE clinical guideline 76)


Algorithm topicals- trunk and limbs
Offer potent corticosteroid applied once daily plus vitamin D or vitamin D analogue applied once daily (applied separately, for example one agent applied in the morning and the other in the evening) for a maximum period of 8 weeks as initial treatment for psoriasis of the trunk and / or limbs in adults.
For children and young people with trunk or limb psoriasis consider either:
calcipotriol applied once daily or
a potent corticosteroid* applied once daily and
Review treatment 2 to 4 weeks after starting treatment.
If once daily application of potent corticosteroids and once daily application of vitamin D or vitamin D analogue does not result in clearance or near clearance or satisfactory control in adults by 8 weeks, offer a vitamin D or vitamin D analogue alone applied twice daily.
If twice daily application of vitamin D or vitamin D analogue does not result in clearance or near clearance or satisfactory control of trunk or limb psoriasis in adults by 8-12 weeks offer either:
potent corticosteroid applied twice daily for up to 8 weeks, or
coal tar preparation applied once or twice daily.
If twice daily potent corticosteroid or coal tar cannot be used and a once daily preparation would improve adherence offer a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily for up to 8 weeks.
Offer treatment with very potent corticosteroids in adults with trunk or limb psoriasis only in secondary care under careful supervision and when other topical treatment strategies have failed and for a maximum period of 4 weeks.
Consider short contact dithranol for treatment-resistant psoriasis of the trunk or limbs and either:
Give educational support for self-use or
Ensure treatment is given in a day care setting.
Offer a review at least annually to people with trunk or limb psoriasis who are using a very potent or potent corticosteroid (either as monotherapy or in combined preparations) to assess for the presence of steroid atrophy and other adverse effects.
Do not use
Consider
Offer


Algorithm for topicals scalp
Offer a potent corticosteroid applied once daily for a maximum period of 8 weeks as initial treatment for people with scalp psoriasis. Choose a low-cost preparation.
Consider topical vitamin D or vitamin D analogues alone for the treatment of scalp psoriasis only in people who are intolerant to or cannot use topical corticosteroids at this site and/or have mild-to-moderate scalp psoriasis.
Show people with scalp psoriasis how to safely apply corticosteroid topical treatment.
If treatment with potent corticosteroid does not result in clearance or near clearance and/or satisfactory control of scalp psoriasis after 4 weeks consider:
a different formulations of the potent corticosteroid (for example, shampoo, mousse) and/or
topical agents to remove adherent scale (for example, those containing salicylic acid, emollients and oils) before further application of the potent corticosteroid.
If the response remains unsatisfactory after a further 4 weeks of treatment offer:
a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily for up to 8 weeks or
vitamin D or vitamin D analogue applied once daily.
If continuous treatment with either a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily or vitamin D or vitamin D analogue for up to 8 weeks does not result in clearance or near clearance and/or satisfactory control of scalp psoriasis offer:
a very potent corticosteroid applied up to twice daily for 2 weeks (up to a maximum of 4 weeks only) for adults only or
coal tar applied once or twice daily or
referral to a specialist for additional support with topical applications and/or advice on alternative treatment options.
Do not offer coal tar based shampoos alone for the treatment of plaque type scalp psoriasis.
Do not use very potent corticosteroids for scalp psoriasis in children.
Do not use
Consider
Offer


Algorithm for topicals – face and flexures (including genitals)
Offer a short term mild or moderate potency corticosteroid applied once or twice daily for people with psoriasis of the face, flexures or genitals (for a maximum of 2 weeks).
Be aware that the face, flexures and genitals are particularly vulnerable to steroid atrophy and that corticosteroids should only be used for short term treatment (1-2 weeks per month).
Explain the risk to people undergoing this treatment and how to minimise them.
For people with psoriasis of the face, flexures or genitals who show an unsatisfactory response to, or require ongoing continuous treatment with short-term moderate potency corticosteroids to maintain control, offer a calcineurin inhibitor applied twice daily for 4 weeks. Calcineurin inhibitors should be initiated by healthcare professionals with expertise in treating psoriasis.
R54: When prescribing active topical agents at facial, flexural and genital sites take into account that they may cause irritation and inform people undergoing treatment of these risks and how to minimise them.
Do not use
Consider
Offer

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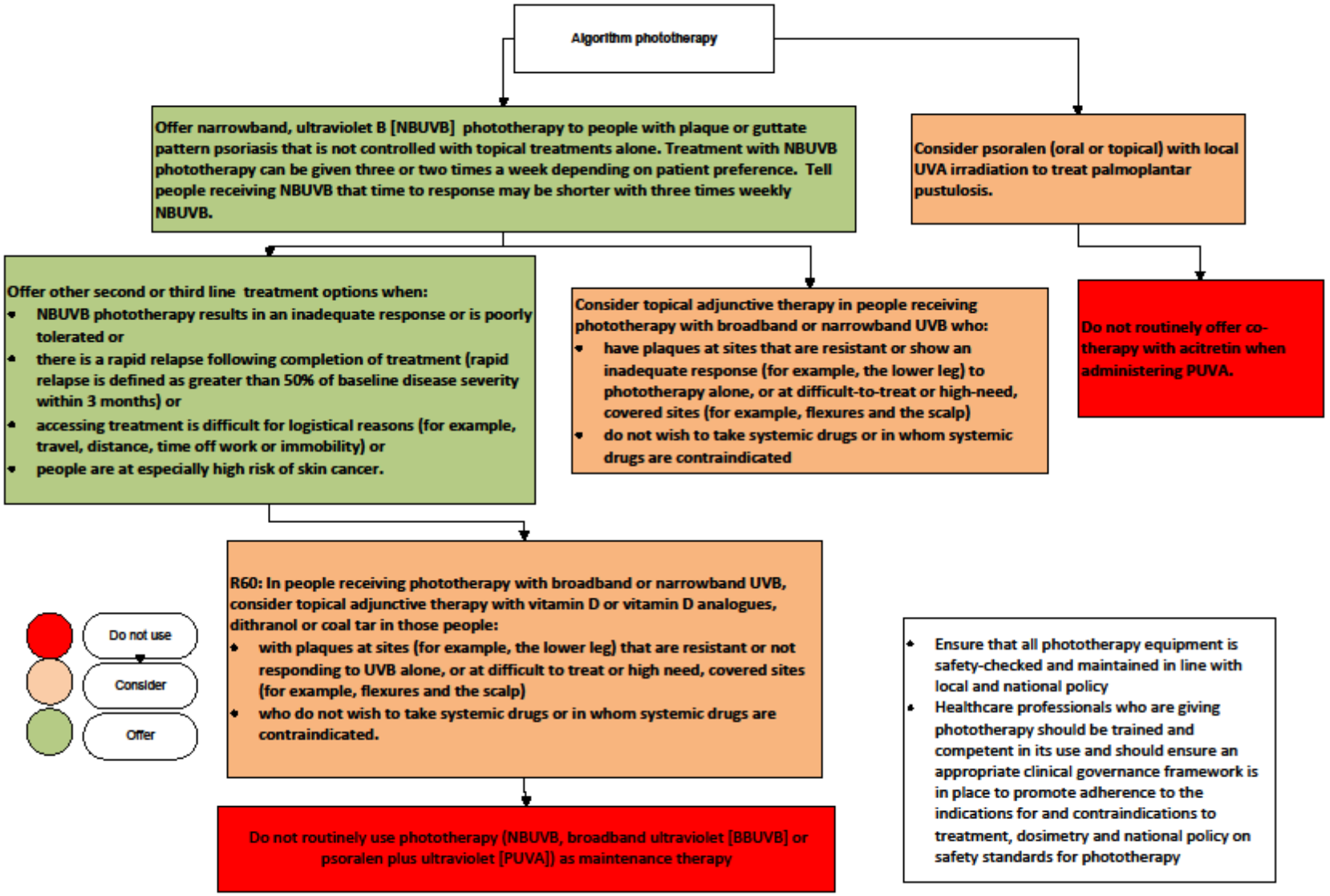
Algorithm phototherapy
Offer narrowband, ultraviolet B [NBUVB] phototherapy to people with plaque or guttate pattern psoriasis that is not controlled with topical treatments alone. Treatment with NBUVB phototherapy can be given three or two times a week depending on patient preference. Tell people receiving NBUVB that time to response may be shorter with three times weekly NBUVB.
Consider psoralen (oral or topical) with local UVA irradiation to treat palmoplantar pustulosis.
Offer other second or third line treatment options when:
NBUVB phototherapy results in an inadequate response or is poorly tolerated or
there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or
accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or
people are at especially high risk of skin cancer.
Consider topical adjunctive therapy in people receiving phototherapy with broadband or narrowband UVB who:
have plaques at sites that are resistant or show an inadequate response (for example, the lower leg) to phototherapy alone, or at difficult-to-treat or high-need, covered sites (for example, flexures and the scalp)
do not wish to take systemic drugs or in whom systemic drugs are contraindicated
Do not routinely offer co-therapy with acitretin when administering PUVA.
Do not use
Consider
Offer
R60: In people receiving phototherapy with broadband or narrowband UVB, consider topical adjunctive therapy with vitamin D or vitamin D analogues, dithranol or coal tar in those people:
with plaques at sites (for example, the lower leg) that are resistant or not responding to UVB alone, or at difficult to treat or high need, covered sites (for example, flexures and the scalp)
who do not wish to take systemic drugs or in whom systemic drugs are contraindicated.
Do not routinely use phototherapy (NBUVB, broadband ultraviolet [BBUVB] or psoralen plus ultraviolet [PUVA]) as maintenance therapy
Ensure that all phototherapy equipment is safety-checked and maintained in line with local and national policy
Healthcare professionals who are giving phototherapy should be trained and competent in its use and should ensure an appropriate clinical governance framework is in place to promote adherence to the indications for and contraindications to treatment, dosimetry and national policy on safety standards for phototherapy

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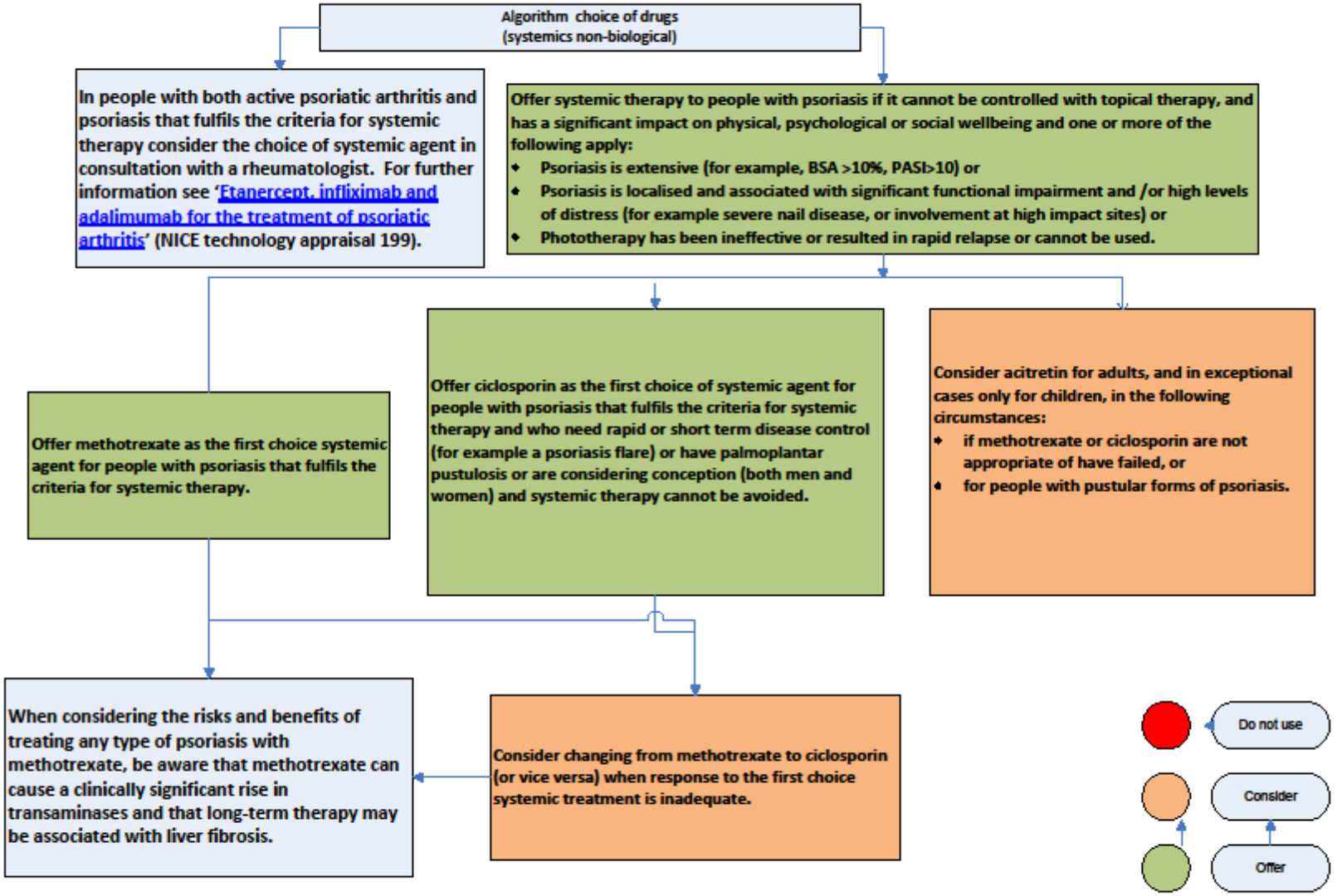
Algorithm choice of drugs
(systemics non-biological)
In people with both active psoriatic arthritis and psoriasis that fulfils the criteria for systemic therapy consider the choice of systemic agent in consultation with a rheumatologist. For further information see 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal 199).
Offer systemic therapy to people with psoriasis if it cannot be controlled with topical therapy, and has a significant impact on physical, psychological or social wellbeing and one or more of the following apply:
Psoriasis is extensive (for example, BSA >10%, PASI>10) or
Psoriasis is localised and associated with significant functional impairment and /or high levels of distress (for example severe nail disease, or involvement at high impact sites) or
Phototherapy has been ineffective or resulted in rapid relapse or cannot be used.
Offer methotrexate as the first choice systemic agent for people with psoriasis that fulfils the criteria for systemic therapy.
Offer ciclosporin as the first choice of systemic agent for people with psoriasis that fulfils the criteria for systemic therapy and who need rapid or short term disease control (for example a psoriasis flare) or have palmoplantar pustulosis or are considering conception (both men and women) and systemic therapy cannot be avoided.
Consider acitretin for adults, and in exceptional cases only for children, in the following circumstances:
if methotrexate or ciclosporin are not appropriate of have failed, or
for people with pustular forms of psoriasis.
When considering the risks and benefits of treating any type of psoriasis with methotrexate, be aware that methotrexate can cause a clinically significant rise in transaminases and that long-term therapy may be associated with liver fibrosis.
Consider changing from methotrexate to ciclosporin (or vice versa) when response to the first choice systemic treatment is inadequate.
Do not use
Consider
Offer

1

6 Principles of care

Self care and self management are central to UK health policy[37] on managing long-term conditions although this may be better described as partnership in care rather than self-care as clinicians still play a significant role in the care process. All patients living with a long-term condition self-manage to a greater or lesser degree. Clinically we are interested in the degree of effective self-management in order to optimise clinical outcomes. Effective self-management relies on three factors: that patients have sufficient understanding of their condition and the treatment prescribed; positive attitudes to self-managing – including belief in their ability to manage and the motivation to do so consistently, as well as the skills to self manage. Simply telling the patient why or showing them how may not be enough to ensure it happens.

When patients are diagnosed with a condition it is usual for them to receive detailed information about their condition, modifiable risk factors and instruction on how to administer medication or treatments, some of which converts to understanding. There is less emphasis on developing appropriate attitudes especially supporting self-efficacy and motivation. Psoriasis is a complex long-term condition that places a particularly high psychological demand on the patient. People experience adverse emotional reactions to the diagnosis, including anxiety and depression and it is perhaps not surprising that any benefits of information and instructions maybe rapidly lost.

Patients own beliefs and attitudes may prevent them from carrying out self-management. Some people lack the confidence to try and others, for a variety of other reasons, simply cannot self-manage. Clinicians often go to great lengths to educate, instruct and support people to take more of a partnership role in the management of psoriasis. However, medicines adherence, as one indicator of individuals' ability to self manage, is reported to be poor in psoriasis, with studies in people with newly-diagnosed psoriasis indicating that 90% do not adhere effectively to topical treatments and 50% do not redeem prescriptions[38].These data suggest that strategies in routine clinical practice may be inadequate with consequent negative impact on outcomes and significant cost to the health service.

Identifying who can self-manage, what support they need and how they learn self management can be difficult in the context of a busy clinic. 'Patient-centred' assessment and tailoring of support can be time consuming and because of this blanket advice may be given that may not achieve the desired. Self-management education programmes are distinct from patient education or skills training, in that they are designed to encourage people with long-term conditions to take a more active part in the management of their own condition. Such programmes have been a key part of diabetes management for some time with consequent improved outcomes[39]. Analogous programmes are not well established in primary or specialist care for psoriasis. The majority of patients access help and support to self manage through consultation with health care professionals, particularly dermatology specialist nurses, standard patient information leaflets and patient support groups such as the Psoriasis Association and PAPPA.

Given the importance of self management in psoriasis, the accepted impact that it has on well being, and the considerable resource already expended on patient education, the GDG posed the following question: what strategies can best support people with psoriasis to self-manage the condition effectively?

6.1 Methodological introduction

A literature search was conducted for RCTs, systematic reviews or cohort studies that addressed the efficacy of self-management strategies (including education packages, interactive programmes and access to nurse specialists) for people with psoriasis. The comparisons considered were any form of self management support compared with standard care or another form of self-management

support. Note that to be included in this review all interventions had to include some component of self-management advice or support and/or access to a dermatology nurse specialist. Therefore, studies using educational interventions that did not address self-management were excluded.

No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded but other similar dermatological conditions were not considered indirect evidence for this non-pharmacological intervention.

The outcomes considered were:

- Patient satisfaction
- Concordance with treatment
- Reduced distress/anxiety/depression (change in HADS)
- Reduced disease severity (e.g., change in PASI, TSS or PGA)
- Reduced stress (change in PLSI)
- Improved quality of life (change in DLQI/PDI)
- Service use

Five studies[40-44] were found that addressed the question and were included in the review:

- Four of these studies[40-42,44] were RCTs
- One study[43] had a prospective cohort design
- No studies were available that assessed self-management exclusively in children with psoriasis

The studies differed in terms of the self-management intervention employed (Table 7).

Table 7: self-management support: interventions of included studies

Ref ID	Population and setting	N	Intervention	Comparison	Follow-up
ERSSER2011	Adults being treated for mild-moderate plaque psoriasis in primary care (only receiving topicals) Pilot study	64	Three components: (i) Structured, nurse-led group learning experience (2 hours); (ii) Supporting written and audiovisual material to provide additional information and a relaxation resource; (iii) Follow-up telephone consultation with nurse (20 minutes).	Normal access to GP (initial visit and follow-up for data collection only)	6 weeks
GRADWELL 2002	Newly referred patients (to dermatologist) aged ≥14 years with a diagnosis of psoriasis or eczema Pilot study	66	20-minute session with dermatology nurse specialist in addition to initial consultation with dermatologist Information was given regarding the skin condition, treatment application, where to receive support and how to get repeat prescriptions; and an individualised treatment programme booklet was provided	Normal care (initial consultation and follow-up with a dermatologist)	6 weeks
KERNICK 2000	Primary care; minimum of 3 repeat prescriptions for	109	Sessions with trained practice nurse (as many as were appropriate)	Routine GP care	4 months

Ref ID	Population and setting	N	Intervention	Comparison	Follow-up
	topicals in the last year; aged 18-65 years; diagnosis of psoriasis or eczema				
MORK 1992A	Chronic, stable, plaque-type psoriasis being treated with dithranol cream as out-patients	29	Additional education: information about the importance of being thorough when rubbing the cream in to the lesions (repeated at each follow-up visit) plus demonstration of correct application by investigator at the first visit	Standard information	6 weeks
RENZI 2006	Adult in- and out-patients attending dermatology clinic for first time for psoriasis	402	Decision board aid to present all the important information on different treatment options in a simple easily comprehensible and visually clear manner.	Routine consultation	Unclear

It was recognised that effective self-management to optimise treatments prescribed whilst preserving quality of life relies on three factors: that patient having sufficient understanding of their condition and of the treatment prescribed; positive attitudes to self-managing, including belief in their ability to manage and the motivation to do so consistently; and the skills to self manage the condition. Therefore, each of the included studies has been summarised to outline the extent to which the intervention addressed each of these three factors (see Table 8). However, the interventions were not described in sufficient detail in any of the studies to accurately determine how well each of the factors for self-management was incorporated.

Table 8: Aspects of self-management in included studies

Study	Aspect of self management included (yes or no)		
	Understanding/knowledge	Attitude/confidence	Skills
ERSSER 2011	Yes • Group-based knowledge sharing • Written and audiovisual materials as supporting information for reference • Follow-up telephone conversation to reinforce concepts	Yes • Individual action planning to support sustained changes in health-related behaviour • Sharing experiences and knowledge with other people with psoriasis • Follow-up telephone conversation to feedback on action plan and provide motivation by discussing future planning	Yes/unclear • Practical element (unclear what this involved)
GRADWELL 2002	Yes • Information provided on the condition, treatment application, where to receive support and how to get repeat prescriptions	Yes • Individualised treatment programme booklet provided to promote a positive and confident attitude to self-management	Yes • Practical demonstrations of treatment application • Instructions on the quantity of treatment to apply based on the fingertip unit or a teaspoon measure
KERNICK 2000	Yes/unclear[(a)] • Trained nurses provided	Unclear	Unclear

Study	Aspect of self management included (yes or no)		
	Understanding/knowledge	**Attitude/confidence**	**Skills**
	consultations to provide education and psychological support		
MORK 1992A	Yes • Information about the importance of being thorough when applying cream to lesions	No	Yes • Demonstration of correct application
RENZI 2006	Yes • Intervention designed to clearly present relevant information about pharmacological interventions to aid patient participation in treatment decisions	No	No

(a) This study was included as it met the protocol criterion of access to a nurse specialist; however, the support provided by the nurses was unclear

6.2 Self-management support (provided by a nurse specialist / trained practice nurse) vs. standard care

6.2.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Standard care + self-management support	Standard care	Relative (95% CI)	Absolute	
Change in DLQI - Mild to moderate disease (follow-up 6 weeks; better indicated by higher values)											
1 Ersser2011	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	none	26	33	-	MD 0.2 lower (1.57 lower to 1.17 higher)	⊕⊕OO LOW
Change in DLQI - Moderate disease (follow-up 6 weeks; better indicated by higher values)											
1 Ersser2011	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	serious[d]	none	9	13	-	MD 1.21 lower (3.90 lower to 1.48 higher)	⊕OOO VERY LOW
Change in DLQI - Mild to severe disease (follow-up 6 weeks; better indicated by higher values)											
1 Gradwell 2002	randomised trials	serious[e]	no serious inconsistency	no serious indirectness[f]	very serious[g]	none	31	31	-	MD 0.27 lower (2.76 lower to 2.22 higher)	⊕OOO VERY LOW
Change in DLQI (follow-up 4 months; Better indicated by higher values)											
1 Kernick 2000	randomised trials	very serious[h]	no serious inconsistency	no serious indirectness[i]	serious[j]	none	46	54	MD 0.9 higher (NS) Nurse / Control Baseline 6.1 ±4.9 / 6.8 ±5.0 4 months 4.6 ±4.7 / 6.2 ±5.2 Change -1.5 / -0.6		⊕OOO VERY LOW
Change in PASI - Mild to moderate disease (follow-up 6 weeks; better indicated by higher values)											
1 Ersser2011	randomised trials	very serious[k]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	none	26	33	-	MD 0.16 higher (0.49 lower to 0.81 higher)	⊕⊕OO LOW
Change in PASI - Moderate disease subgroup (follow-up 6 weeks; better indicated by lower values)											

1 Ersser2011	randomised trials	very serious[l]	no serious inconsistency	no serious indirectness	serious[d]	none	9	13	-	MD 0.82 higher (0.7 lower to 2.34 higher)	⊕OOO VERY LOW
Change in disease severity (follow-up 4 months; measured with: clinical score (range 0-15); better indicated by lower values)											
1 Kernick 2000	randomised trials	very serious[m]	no serious inconsistency	no serious indirectness[i]	serious[j]	none	46	54	MD 1.4 higher (p<0.05) Nurse Control Baseline 9.3 ±2.9 8.4 ±3.1 4 months 7.6 ±3.3 8.1 ±3.3 Change -1.7 -0.3		⊕OOO VERY LOW
Treatment concordance/knowledge - How much treatment to apply (follow-up 6 weeks)											
1 Gradwell 2002	randomised trials	serious[n]	no serious inconsistency	serious[o]	no serious imprecision	none	28/28 (100%)	24/26 (92.3%)	RR 1.08 (0.95 to 1.23)	74 more per 1000 (from 46 fewer to 212 more)	⊕⊕OO LOW
Treatment concordance/knowledge - How long to apply for (follow-up 6 weeks)											
1 Gradwell 2002	randomised trials	serious[p]	no serious inconsistency	serious[o]	serious[q]	none	28/28 (100%)	23/27 (85.2%)	RR 1.17 (0.99 to 1.39)	145 more per 1000 (from 9 fewer to 332 more)	⊕OOO VERY LOW
Additional service use required - % follow-up appointments conducted by nurse (follow-up 6 weeks)											
1 Gradwell 2002	randomised trials	serious[r]	no serious inconsistency	no serious indirectness	very serious[s]	none	Unclear	Unclear	Nurse: 33% Control: 0%		⊕OOO VERY LOW
Additional service use required - Number needing GP visit during follow-up (follow-up 6-24 weeks)											
2 Gradwell 2002 Kernick 2000	randomised trials	serious[t]	no serious inconsistency[u]	no serious indirectness[v]	no serious imprecision	none	5/74 (6.8%)	25/82 (30.5%)	RR 0.22 (0.09 to 0.54)	238 fewer per 1000 (from 140 fewer to 277 fewer)	⊕⊕⊕O MODERATE

(a) Inadequate randomisation, unclear allocation concealment, more females in the intervention group and small pilot study
(b) Precise according to GDG discussion (confidence interval lies completely within effect estimates that indicate no clinically important benefit)
(c) Post-hoc subgroup analysis, inadequate randomisation, and unclear allocation concealment, more females in the intervention group and small pilot study
(d) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important difference to no clinically important difference)
(e) Not matched at baseline (higher age, disease severity and DLQI in normal care group at baseline - difference in DLQI of greater magnitude than mean difference in change). Also unclear which topical interventions used (and unclear if the same in each group)
(f) Mixed population (46% psoriasis), but it is unlikely that the psoriasis and eczema populations would respond differently to the intervention
(g) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect
(h) Unclear allocation concealment, high differential drop-out rate (36% in intervention - including 16% who refused first appointment - and 15% in control); not matched at baseline for sex and disease severity. Also, unclear what topicals used and if the same in each group
(i) Mixed population (41% psoriasis), but it is unlikely that the psoriasis and eczema populations would respond differently to the intervention

(j) No estimate of variance provided
(k) Inadequate randomisation and unclear allocation concealment, unblinded, more females in the intervention group and small pilot study
(l) Post-hoc subgroup analysis, inadequate randomisation, unblinded and unclear allocation concealment, more females in the intervention group and small pilot study
(m) Unclear allocation concealment, unblinded, high differential drop-out rate (36% in intervention - including 16% who refused first appointment - and 15% in control); not matched at baseline for sex and disease severity. Also, unclear what topicals used and if the same in each group
(n) Differential drop-out rate (21% in control group and 15% in intervention group). Also unclear which topical interventions used (and unclear if the same in each group) and not matched at baseline (older and more with moderate to severe disease in control group, although this is unlikely to bias this outcome)
(o) Surrogate outcome for treatment concordance and mixed population (46% psoriasis), but it is unlikely that the psoriasis and eczema populations would respond differently to the intervention
(p) Unclear which topical interventions used (and unclear if the same in each group) and not matched at baseline (older and more with moderate to severe disease in control group, although this is unlikely to bias this outcome)
(q) Confidence interval ranges from clinically important effect to no effect
(r) Not matched at baseline (higher age, disease severity and DLQI in normal care group at baseline). Also unclear which topical interventions used (and unclear if the same in each group)
(s) No estimate of variance available and number requiring follow-up visit in each group unclear
(t) 1/2 unclear allocation concealment, 1/2 high differential drop-out rate (36% in intervention - including 16% who refused first appointment - and 15% in control), 1/2 not matched at baseline (higher age, disease severity and DLQI in normal care group at baseline), 2/2 unclear what topicals used and if the same in each group
(u) Different healthcare settings for the intervention in the two trials (primary and secondary care)
(v) Mixed population (41-46% psoriasis), but it is unlikely that the psoriasis and eczema populations would respond differently to the intervention

6.2.2 Evidence statements

In people with psoriasis or eczema, additional self-management support (provided by a nurse specialist/trained practice nurse) was statistically significantly better than standard care for:

- Change in disease severity at 4 months [1 study; 100 participants; very low quality evidence][42]
- Number needing GP visit during follow-up at 6 weeks or 4 months [2 studies; 156 participants; moderate quality evidence][41,42]

In people with psoriasis or eczema, there was no statistically significant difference between additional self-management support (provided by a nurse specialist/trained practice nurse) and standard care for:

- Change in DLQI at 6 weeks or 4 months (all disease severities) [3 studies; 221 participants; low to very low quality evidence][41,42,44]
- Change in PASI at 6 weeks (mild-moderate or moderate disease) [1 study; 59 participants; low to very low quality evidence][44]
- Treatment concordance/knowledge (how much treatment to apply and how long to apply for) at 6 weeks [1 study; 54-55 participants; low to very low quality evidence][41]

Evidence statement for individual study where no statistical analysis could be performed:

- One study demonstrated that a notable proportion of scheduled follow-up appointments with a dermatologist could be performed by a nurse specialist who had been involved in providing self-management support (33% compared with 0% follow-up visits with a dermatologist able to be cancelled in the

normal care group) [1 study; 100 participants; very low quality evidence][41]
It was unclear how many participants in each group would have attended for follow-up visits.

6.2.3 Subgroup analysis

One study[44] performed a post-hoc subgroup analysis including only those people with psoriasis who had moderate disease severity, defined as PASI or DLQI >6 points, which resulted in a small sample size. As with the full sample, there was no significant difference for this subgroup on the outcome of either change in PASI or change in DLQI between the group receiving standard care and the group receiving additional self-management support provided by a nurse specialist. However, a trend towards favouring the group with additional self-management support for change in PASI was more apparent in these individuals with greater disease severity or impact at baseline than in the full group, which included many people with PASI<3. Conversely, the change in DLQI was non-significantly greater in the standard care group.

6.2.4 Additional application information vs. standard information for use of dithranol

6.2.4.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Additional application information	Standard information	Relative (95% CI)	Absolute	
% change in TSS (follow-up 6 weeks; Better indicated by higher values)											
1 Mork 1992	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	15	14	-	MD 28 higher (p<0.05) **Control** **Extra info** Baseline 1.98 1.91 % reduction 39% 67%	⊕⊕OO LOW

(a) Unclear allocation concealment, no blinding, unclear baseline comparability
(b) No estimate of variance provided

6.2.4.2 Evidence statements

In people with psoriasis being treated with dithranol cream, additional information about application was statistically significantly better than standard information for:

- Percentage change in disease severity (TSS) at 6 weeks [1 study; 29 participants; low quality evidence][40]

6.2.5 Decision board aid vs. standard consultation

6.2.5.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decision board	Standard consultation	Relative (95% CI)	Absolute	
Satisfaction with care - Overall satisfaction with care											
1 Renzi 2006	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	144/231 (62.3%)	114/171 (66.7%)	RR 0.94 (0.81 to 1.08)	40 fewer per 1000 (from 127 fewer to 53 more)	⊕OOO VERY LOW
Satisfaction with care - Satisfaction with decision making											
1 Renzi 2006	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/231 (63.2%)	107/171 (62.6%)	RR 1.01 (0.87 to 1.18)	6 more per 1000 (from 81 fewer to 113 more)	⊕OOO VERY LOW
Satisfaction with care - Opportunity to express opinions											
1 Renzi 2006	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107/231 (46.3%)	83/171 (48.5%)	RR 0.95 (0.78 to 1.17)	24 fewer per 1000 (from 107 fewer to 83 more)	⊕OOO VERY LOW
Satisfaction with care - Information on treatment options											
1 Renzi 2006	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/231 (54.5%)	98/171 (57.3%)	RR 0.95 (0.8 to 1.13)	29 fewer per 1000 (from 115 fewer to 75 more)	⊕OOO VERY LOW
Satisfaction with care - Information on treatment side effects											
1 Renzi 2006	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	118/231 (51.1%)	42/171 (24.6%)	RR 2.08 (1.55 to 2.78)	265 more per 1000 (from 135 more to 437 more)	⊕OOO VERY LOW

(a) *Failure to measure all prognostic factors or adjust for confounders in statistic analysis*

6.2.16 Evidence statements

In people with psoriasis, additional information about treatment options by means of a decision board was statistically significantly better than standard information for:

- Satisfaction with information about side effects [1 study; 402 participants; very low quality evidence][43]

In people with psoriasis, there was no statistically significant difference between additional information about treatment options by means of a decision board and standard information for:

- Overall satisfaction with care [1 study; 402 participants; very low quality evidence][43]
- Satisfaction with decision making [1 study; 402 participants; very low quality evidence][43]
- Satisfaction with opportunity to express opinions [1 study; 402 participants; very low quality evidence][43]
- Satisfaction with information on treatment options [1 study; 402 participants; very low quality evidence][43]

6.3 Cost effectiveness evidence

One study[42]was included that included a relevant comparison. This is summarised in the economic evidence profile below. See also the full study evidence tables in Appendix I. No studies were excluded.

Table 9: Dermatology nurse led clinic vs routine GP care – Economic study characteristics

Study	Limitations	Applicability	Other comments
Kernick 2000[42] (UK NHS)	Very serious limitations (a)	Partially applicable (b)	Cost-consequence analysis

(a) Costs are not aggregated and presented as mean/median cost per patient; costs of topicals and any other treatments administered not included; unit costs are out of date for current decision-making; no incremental analysis could be performed for costs; no sensitivity analyses were undertaken; funded by Leo Pharmaceuticals, makers of vitamin D analogues and combined vitamin D analogue and potent corticosteroid products.

(b) The population is a mixture of patients with psoriasis and eczema

Table 10: Dermatology nurse led clinic vs routine GP care – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Kernick 2000[42] (UK NHS)	NR	0.0062 QALYs	NA	

This cost-consequence analysis is not ideal for assessing the cost-effectiveness of dermatology nurse-led clinics, but some useful information can be gleaned from it. First, it appears that nursing input may improve health-related quality of life of patients with skin conditions such as eczema and/or psoriasis more than routine GP care; however, there is a great deal of uncertainty in this finding. Given the large standard errors around the mean quality of life at baseline and at the end of 4-month follow-up, the difference between interventions in terms of quality of life improvement does not reach significance.

Even given the uncertainty, it is worthwhile to consider what increase in cost might be acceptable given the mean QALY gain and the NICE willingness to pay threshold. If the QALY gain is 0.0062 for nurse input compared to routine GP care, then at a willingness to pay threshold of £20,000 per QALY gained, nurse input would only be cost-effective if it cost less than £123 more over 4 months than

routine GP care. At a threshold of £30,000 per QALY gained, the cost difference could increase up to £186 and be considered cost-effective.

The authors do not cost the intervention in terms of actual resource use or cost per patient, but rather look at the likely annual cost in terms of nursing time spent training and delivering the intervention. They make the assumption that training a practice nurse requires 87 hours per year and that delivering the intervention will require 138 hours per year. They assume that a practice nurse would run a dermatology clinic once per week and see nine patients during each clinic. Their data also showed that 84% of patients visited the nurse led clinic for a median of two visits over the 4-month study period.

Based on these data and assumptions, using 2010 unit costs[45] and including nurse training and clinic time, the total cost works out to roughly £27 per patient[b]. If patients continued to use the nurse led dermatology service with the same frequency, then this would translate to 6 visits annually at a cost of approximately £80 per patient.

Unfortunately, the authors do not give much information about the resource use in the routine GP care group. They merely state that 25% of patients (14/54) saw their GP at least once during the 4-month follow-up. Using 2010 unit costs for a GP consultation (£28), this would translate to a per-patient cost of around £7. This means that the cost difference over 4 months between interventions is likely to be £20 which is well below the £123 ceiling at which it might be cost-effective at a willingness to pay threshold of £20,000 per QALY. However, given the aforementioned uncertainty, it is possible that dermatology nurse input could generate lower QALY gain than routine care. In this circumstance, nurse input would be more costly and less effective and would not be a worthwhile use of NHS resources.

One key component of cost that the study does not capture are those costs that might be avoided as a result of introducing nurse support, e.g. reduced GP consultations, more effective use of topicals, etc. It is possible that these offsets could improve the cost-effectiveness of dermatology training and dedicated nursing support.

6.3.1 Evidence statements

- One cost-consequence analysis suggested that providing a structured training programme for practice nurses and then having a nurse led clinic was more costly and might improve health outcomes in terms of gains in health-related quality of life compared to routine GP care. As there is considerable uncertainty in the benefit gained from having this nurse led service, only a very modest increase in cost is likely to be justified. This is based on evidence with very serious limitations and partial applicability.

6.4 Recommendations and link to evidence

Recommendations on principles of care	**1. Offer people with all types of psoriasis support and information tailored to suit their individual needs and circumstances, in a range of different formats so they can confidently understand:** • **their diagnosis and treatment options** • **lifestyle risk factors that are relevant** • **how to recognise a flare**

b Calculated based on the following assumptions: 75 hours per 4 month period (29 for training and 46 in clinic); 4.33 hours per week (1.67 for training and 2.65 for clinic); 9 patients per clinic; 11.4 minutes nurse training + 18 minutes per patient per clinic attendance; £29 per practice nurse hour of in clinic and £26 per practice nurse hour generally; patients attend dermatology nurse clinic twice in 4 months.

	• **how to use prescribed treatments safely and effectively (for example, how to apply topical treatments and how to minimise the risk of side effects through safe monitoring of medicines)** • **when and how to seek further general or specialist review** • **strategies to deal with the impact of psoriasis on physical, psychological and social wellbeing.** **2. When offering treatments to a person with any type of psoriasis:** • **ensure the treatment strategy is developed to meet the individual's health goals so that the impact of their condition is minimised and use relevant assessment tools to ensure these goals are met** • **take into account the age and individual circumstances of the person, disease phenotype, severity and impact, co-existing psoriatic arthritis, comorbidities and previous treatment history** • **discuss the risks and benefits of treatment options with the person and where possible include use of absolute risk and natural frequency.** **3. Assess whether support and information needs updating or revising at every review or interaction with the person affected, in partucular during transition from children's services to adult services, when new interventions become available, and when the person's disease severity or circumstances change.** **4. Provide a single point of contact to help people with all types of psoriasis access appropriate information and advice about their condition and the services available at each stage of the care pathway.** **5. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in 'Patient experience in adult NHS services' (NICE clinical guideline 138). Recommendations on shared decision making, including discussions about investigation or treatment options and risks and benefits can be found in section 1.5 of that guideline.**
Future research recommendations	**1. Do structured psoriasis focussed educational programmes improve patient confidence, well-being and disease control as compared to standard care?**
Relative values of different outcomes	The following outcomes were included: • Patient satisfaction • Concordance with treatment • Reduced distress/anxiety/depression (HADS score) • Reduced disease severity (PASI, TSS or PGA) • Reduced stress (PLSI) • Improved quality of life (DLQI, PDI)

	• Service use
Trade off between clinical benefits and harms	None of the studies that reported change in DLQI demonstrated a clinically relevant benefit of self-management, although the GDG discussed that this may have been due to insufficient sample size and follow-up. Similarly, there was no clinically relevant difference in change in PASI between those who had access to additional self-management support and those receiving only standard care. However it was noted that PASI is less sensitive for assessing changes in mild disease, while change in disease severity assessed on a 0-15 scale (similar to the total severity score) showed a significant difference in favour of the group receiving self-management support. Treatment knowledge was improved by the interventions to support self-management, but the number with adequate knowledge was also high in the standard care group. There was also a suggestion that access to self-management support may reduce the need for service use. The GDG agreed that the available evidence was insufficient in terms of quality and quantity to accurately weight the benefits and harms or to inform a recommendation.
Economic considerations	Economic evidence to inform the GDG on the cost-effectiveness of strategies to promote or improve self-management of disease among patients with psoriasis was minimal and generally had limitations. There was too much uncertainty in the clinical effectiveness for the GDG to make any recommendations in favour of a specific strategy. The GDG considered that effective self-management by patients was likely to generate efficiencies in the care of people with psoriasis. If patients are advised about when and how to effectively re-initiate treatments, for example topicals, it may hasten improvements in their quality of life and reduce the need for consultation with GPs and/or dermatologists. Advice on the effective application of topicals is likely to improve treatment outcomes and could potentially reduce the need for treatment change and/or onward referral to a specialist. The GDG considered that extra time spent discussing these concepts and advising on when to seek additional help would not represent much in the way of additional NHS costs, but could substantially improve patient outcomes and make effective use of resources.
Quality of evidence	The evidence base is generally poor and no direct evidence was found for concordance with treatment, distress, anxiety, depression or stress. Regarding the self-management intervention employed in each of the studies, the most comprehensive strategies, covering each of the three key components of self-management (knowledge/understanding, attitudes/confidence and skills) were the Ersser and Gradwell studies, both of which were designed to have nurse specialists administering the self-management support. However, both of these studies were pilot studies not adequately powered to show a difference between the additional self-management support and standard care groups. Additionally, the Ersser study had poor recruitment (64 of 340invited to participate were included) and the two groups were not matched at baseline for gender, although the GDG thought this was unlikely to bias the results and gender differences are likely to be limited; although as

	there were fewer males in the self-management group this may suggest that females are more likely to opt-in to such programmes. The Gradwell study also lacked baseline comparability between the two groups, with the age, disease severity and DLQI being higher in the standard care group. Cluster randomisation was used in the Ersser study (randomised according to treatment centre as opposed to per patient), which helps avoid cross contamination, but has the limitation that individuals within a particular group tend to be more similar to each other than to members of other groups. The study reported having performed an appropriate multi-level model to account for this but did not present the results from this, stating that they did not differ from the standard, unadjusted analysis. However, insufficient data were reported for this to be independently calculated and confirmed and lack of adjustment for intra-group correlation may lead to a unit of analysis error and produce over-precise results. The results from this study were not meta-analysed with other studies so inappropriate weighting will not have occurred. The Kernick study had reporting limitations regarding information about the self-management intervention, which included sessions with a trained practice nurse. However, the number of sessions and the information provided were unclear, which made it difficult for the GDG to determine what aspect of self-management may be important in bringing about the benefit seen over the standard care group. It was also unclear what topical treatment was used and whether this was the same for both groups, which may have confounded the results if the pharmacological interventions were different as any difference in outcomes may not be attributable to the additional self-care support. Furthermore, the study had a higher drop-out rate and higher baseline disease severity in the intervention group. The Mork study, related to a very specific aspect of self-management, as it only addressed the benefit of being clear about and reinforcing the need to be thorough when rubbing in dithranol, so the GDG agreed that it may not be possible to generalise further from this study. It also had the limitations of a small sample size (n = 29) and not reporting what standard information was provided in the control group. The decision board used in the Renzi study to aid the involvement of patients in the decision-making process and so engage them with their treatment plan appeared, from the limited description provided, to be mostly concerned with adverse events associated with treatments and the decision board itself was not provided. This study also reported only unadjusted, observational data that could have been biased by confounding factors that were not controlled for and it was unclear whether there were important differences at baseline in this non-randomised study. Overall the quality of the studies was limited and the GDG were unable to draw conclusions from them about which aspects or specific elements of self-care made a difference to the outcomes reported.
Other considerations	• Two of the studies that employed nurse specialists to administer the self-management support were undertaken in primary care settings (Ersser and Kernick) while one was performed in secondary care

	(Gradwell) • The Ersser study included a higher proportion of older people. The DLQI is less applicable to older people as some of the fields are not relevant. • Practice nurse training for 87 hours to enable them to provide support to patients to self-manage their condition effectively, as in the Kernick study, is unrealistic. • Decision boards may help patients to weigh up the risks and benefits of different treatments. The GDG noted the potential for misuse of decision boards – it could be used as a substitute for a proper discussion with the patient. The patient may not be engaged by this type of intervention and this would defeat the purpose of using the decision board. • Practicability of providing additional self-care information during a GP appointment – additional GP knowledge and time would be needed.

1

7 Assessment and referral

7.1 Assessment tools for disease severity and impact and referral for specialist care

Holistic assessment of patients presenting to any health care professional for help is fundamental to good clinical practice and should encompass the psoriasis itself and the impact the disease has on the individual's well being. Both dimensions are important, and different.

This assessment, self evidently, involves talking to the patient and performing a clinical examination and will vary in detail and extent depending on the clinical context. Formal measurement of disease and impact does not replace the need for this activity, but can provide useful, complimentary information to inform clinical decision making, plan treatment and to evaluate the effectiveness of any intervention. At a health care organisation level, measurable aspects of disease severity and impact can be used to inform the development of treatment pathways that allow equality and ease of access to the relevant treatment in the appropriate clinical setting and to facilitate audit to ensure high quality health care and improved patient outcomes. Objective evaluation of treatment efficacy at appropriate time points also facilitates cost effective use of health resources by ensuring ineffective treatments are discontinued.

Currently there are no biomarkers for disease activity in psoriasis so 'measurement' is based on clinical evaluation of the skin by trained individuals. Many tools have been developed[46], but by far the one most commonly used in clinical practice is the Psoriasis Area and Severity Index (PASI). This estimates disease severity by assigning numerical values to qualitative assessments of redness, scale and thickness of psoriatic plaques at individual body sites, as well as estimates of the affected body surface area. It is a non-linear measure (range 0-72) and scores of 10 or more have been shown to correlate with a number of indicators of severe disease such as needing hospital admission or use of systemic therapy. There are problems associated with the PASI in that it is non linear, lacks sensitivity to change when body surface area <10% and the three features (erythema, scale, induration) are co-dependent. It has not been validated in children or very young children where assessments for body surface area are especially likely to be inaccurate[47] and its clinical utility is limited to plaque-type disease.

For non plaque types of psoriasis, body surface area assessment is sometime used, although is considered subject to inaccuracies, and inter individual variation; photography remains widely used for localised types of psoriasis such as acrodermatitis pustulosis. For patients with psoriatic arthritis and psoriasis, different assessment tools are used for each compartment (see also section 6.2) and the lack of a score that combines both is a recognised limitation.

Assessment of the impact of psoriasis on an affected persons' wellbeing (including health-related quality of life [HRQoL]) is crucial, and can be underestimated by clinicians managing skin disease, even in specialist settings. Psoriasis can be a highly stigmatising condition. It contributes to low self-esteem, depression, relationship breakdown and absence from the workplace, and has an impact on HRQoL that is comparable to other major medical conditions[48]. The most commonly used measure of impact is the skin specific tool known as the Dermatology Life Quality Index (DLQI, range 0-30) although this may not be sensitive enough to an important aspect of wellbeing: low mood and depression. The DLQI has been validated in a variety of skin conditions including psoriasis and a DLQI score of more than 10 is considered to correlate with 'a very large effect' on life quality and 5 or less with everyday life stress. It is available in 55 languages, and has become an accepted, validated measure of psoriasis impact in clinical practice, trials and regulatory agencies. It has been criticised for incomplete capture of the psychological impact of skin disease, and significant item bias such that external factors such as age, sex and nationality impact on scores[49]. Newer skin specific tools such as

Skindex-17 (an amended version of Skindex-29) and psoriasis specific -tools have been developed but are not routinely used in clinical practice. The development of accurate disease impact tools for psoriasis in limited but sensitive areas of the body is an area for further research.

Disease severity and impact metrics were not in routine clinical or trial use prior to the emergence of biological therapies around 2005. Historically clinicians and patients used narrative to describe disease status and treatment response supplemented with photography in specialist practice. With the introduction of biological therapies, the British Association of Dermatologists Guidelines Group[2] and NICE recommended use of formal tools (Psoriasis Area and Severity Index, PASI, and Dermatology Life Quality Index, DLQI to assess disease severity and impact, respectively) to assess patients with plaque psoriasis being considered for biological therapy and to establish treatment efficacy.

Largely as a result of this, dermatologists and nursing staff in specialist practice (level 3 and 4)[12] are trained in the use and interpretation of PASI and DLQI, and whilst the standard assessment for patients requiring biological therapy mandates PASI and DLQI assessment (to secure NICE funding approval), this has led to the more widespread use of these tools for those requiring phototherapy or systemic therapy. In primary care, and non specialist settings (level 2) assessment of psoriasis generally follows the traditional history and skin examination with little use of formal assessment tools.

Given the clinical value of formal assessment of psoriasis to both individual patient care and in facilitating cost effective, high quality health care delivery, the accepted shortfalls in the tools established in specialist biological practice (PASI and DLQI) and the absence of guidance on the assessment of psoriasis in primary and secondary care, the GDG agreed to ask the following question: In people with psoriasis (all types), which are the most effective tools to assess the (a) severity and (b) impact of disease across all levels of healthcare provision and at any stage of the disease journey?

7.2 Methodological introduction

A literature search was conducted for studies in people with psoriasis addressing the validity and reliability of any psoriasis-specific tools (validated or non-validated), or dermatology-specific tools that have been validated for use in psoriasis. Tools that are not specific to dermatological conditions were excluded in order to focus on those most relevant to the psoriasis population and owing to the large number of generic assessment tools available.

All settings were included because information regarding the most appropriate tests at all levels of healthcare provision was sought and subgroup information was included, where available, for the validity and reliability of tools to assess psoriasis at specific body sites.

No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The outcomes considered were:

- Construct validity
- Internal consistency
- Inter-rater/observer reliability
- Intra-rater or test-retest reliability
- Practicability
- Sensitivity to change

Definitions of these measures are given in Table 11.

7.3 Definitions of outcomes

Table 11: Definitions of outcome measures used in this review question and categorisation into adequate and acceptable values

Outcome	Definition	Adequate	Acceptable	Poor
Construct validity	Does the scale measure the hypothetical construct (disease severity or impact) that it should measure? *Convergent:* do two scales that are predicted to be measuring the same construct show high correlation. *Divergent:* do two scales that are predicted to be measuring different constructs show low correlation.	Convergent: correlation ≥ 0.70 Divergent: correlation <0.70 Agreement for categorical variables: κ >0.80	Convergent: correlation = 0.60-0.69 Divergent: correlation = 0.71-0.85 Agreement for categorical variables: κ = 0.61-0.80	Convergent: correlation = <0.60 Divergent: correlation = >0.85 Agreement for categorical variables: κ < 0.61
Internal consistency	Are the different domains/items of the scale inter-related?	Cronbach's α ≥ 0.70	Cronbach's α = 0.60-0.69	Cronbach's α < 0.60
Test-retest/intra-rater reliability*	Do two assessments performed by the same investigator produce the same result?	ICC >0.9 % variation <5% Coefficient of variation <10%	ICC = 0.8-0.9 % variation 5-10% Coefficient of variation 10-20%	ICC < 0.8 % variation >10% Coefficient of variation >20%
Inter-rater reliability*	Do two or more different investigators achieve the same result?	ICC >0.80 Coefficient of variation <20% ANOVA (% variance explained by observer) <10%	ICC = 0.60-0.80 Coefficient of variation 20-30% ANOVA 10- 20%	ICC = <0.60 Coefficient of variation >30% ANOVA > 20%
Sensitivity to change*	Can clinically relevant changes be detected by this tool?	ICC > 0.80	ICC = 0.60-0.80	ICC < 0.60
Acceptability /practicability	Is the tool practical enough to be applied in everyday clinical practice?	Time to administer -routine clinical practice <3 min -clinical trials <7 min	Time to administer -routine clinical practice 3-5 min -clinical trials 7-10 min	Time to administer -routine clinical practice >5 min -clinical trials >10 min

**Note that the ICC statistic is the best for these outcomes and other correlation coefficients are not appropriate*

Source: E. Puzenat, V. Bronsard, S. Prey, P. A. Gourraud, S. Aractingi, M. Bagot, B. Cribier, P. Joly, D. Jullien, M. Le Maitre, C. Paul, M. A. Richard-Lallemand, J. P. Ortonne, and F. Aubin. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. J.Eur.Acad.Dermatol.Venereol. 24 (Suppl 2):10-16, 2010. [50]*; P. I. Spuls, L. L. Lecluse, M. L. Poulsen, J. D. Bos, R. S. Stern, and T. Nijsten. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. J.Invest.Dermatol. 130 (4):933-943, 2010.* [46]

The tools included in the search are listed below and defined in **Error! Reference source not found.**.

- Physician assessment of severity:
  - Body surface area affected (BSA) – 6 studies reviewed
  - Copenhagen Psoriasis Severity Index (CoPSI) – 1 study reviewed
  - Global Severity Score (GSS) – 0 studies reviewed
  - Head And Neck PASI (HN-PASI) – 0 studies reviewed
  - Lattice-System Physician's Global Assessment (LS-PGA) – 3 studies reviewed
  - Nail Psoriasis Severity Index (NAPSI) – 2 studies reviewed
  - Photography – 2 studies reviewed
  - Physician's global assessment (PGA): static score – 8 studies reviewed
  - Physician's Global Assessment (PGA): dynamic score – 2 studies reviewed
  - Psoriasis Area and Severity Index (PASI) – 23 studies reviewed
  - Psoriasis Scalp Severity Index (PSSI) – 0 studies reviewed
  - Salford Psoriasis Index (SPI) – 3 studies reviewed
  - Scalp-Modified PASI (s-mPASI) – 0 studies reviewed
  - Scalp-Specific Patient's Global Assessment (S-PaGA): dynamic – 0 studies reviewed
  - Target plaque scores – 0 studies reviewed
- Patient assessment of severity:
  - Self-administered PASI (SAPASI) – 10 studies reviewed
  - Body surface area affected – Patient Report of Extent of Psoriasis Involvement (PREPI) – 1 study reviewed
- Impact:
  - Children's Dermatology Quality of Life Index (CDLQI) – 0 studies reviewed
  - Dermatology Quality of Life Scales (DQOLS) – 1 study reviewed
  - Dermatology Quality of Life Index (DLQI) – 6 studies reviewed
  - Impact of Psoriasis Questionnaire (IPSO) – 2 studies reviewed
  - Psoriasis Disability Index (PDI) – 6 studies reviewed
  - Psoriasis Index of Quality of Life (PSORIQoL) – 2 studies reviewed
  - Psoriasis Life Stress Inventory (PLSI) – 3 studies reviewed
  - Psoriasis Quality of Life Questionnaire (PQoL-12) – 1 study reviewed
  - Questionnaire on Experience with Skin Complaints (QES) – 0 studies reviewed
  - Salford Psoriasis Index (SPI) – 3 studies reviewed
  - Scalpdex – 0 studies reviewed
  - Skindex-17 – 0 studies reviewed
  - Skindex-29 – 2 studies reviewed
  - The Dermatology Specific Quality Of Life Instrument – 0 studies reviewed

Although PASI may be seen as a gold standard tool for assessment of disease severity, it is widely thought to have limitations and so all tools have been compared with each other.

Table 12: Disease severity and impact assessment tools

Instrument	Description
Severity	

Instrument	Description
BSA	Estimation of involved body surface area, several scores are used
CoPSI	Erythema, plaque thickness and scaling are scored 0-4 at each of 10 sites: face, scalp, upper limbs (excluding hands and wrists), hands and wrists, chest and abdomen, back, buttocks and sacral area, genitalia, lower limbs (excluding foot and ankle), feet and ankles. The average at each site is recorded and summed (range 0-81 (excluding genitalia) or 0-90 for full assessment)
GSS	Similar to PGA; scale of the severity of psoriasis
HN-PASI	Erythema, plaque thickness and scaling are scored 0-4 for the head and neck. The sum of the 3 parameters are multiplied by an assessment (range 1-6) of the extent of scalp psoriasis and multiplied by a constant factor 0.1 (to reflect that the head/neck region is 10% of the body surface area). Maximum score is 7.2.
LS-PGA	Combines the percentage body surface area coverage (7-point scale) and average of plaque qualities of thickness, erythema and scale (4 point scale). The two scores are combined in a lattice to give an overall rating from clear to very severe.
Nail Psoriasis Severity Index (NAPSI)	Each nail is split into 4 quadrants and each is scored 0 or 1 for each of the following: pitting, leukonychia, red spots, nail plate crumbling, onycholysis, splinter haemorrhage, oil drop and nail bed hyperkeratosis. The total score for each quadrant can be up to 8 and the overall score for each nail is out of 32.
PASI	Each body area (head, upper limbs, lower limbs and trunk) is given a score out of 0-4 (0=clear, 4= very severe) for erythema, thickness and scaling (individually). The subtotal score (0-12) for each body area is then multiplied by the percentage of the body region affected score (graded 0-6). This score is multiplied by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively (in accordance with the weightings of these areas) and the total score is the sum of the body areas (range: 0-72)
PGA - dynamic	The dynamic PGA is a 5, 6, or 7-point ordinal rating ranging from “worse” to “cleared”
PGA - static	The static PGA is a 5, 6, or 7-point ordinal rating ranging from “clear” to “very severe psoriasis”
PREPI	The patient is asked to estimate how many palm areas it would take to cover up all the patches of psoriasis
PSSI/s-mPASI	Erythema, induration and desquamation scored 1-4 for the scalp.
SAPASI	A version of the PASI that is assessed by the patient. Head, upper extremities, trunk, lower extremities each scored from 0-6 (0=0% affected, 6=91-100%) and each area has its own multiplier (0.1, 0.2, 0.3, 0.4 respectively). The total of theses scores is added to scores for colour, thickness and scaliness and the total is divided by the length of the visual analogue scale (how bad your psoriasis is today, draw a line, measured in mm). This total is then multiplied by 4 to give your total score (0-4 scale)
S-PaGA	5 point scalp specific dynamic scale. Range: -2 much worse, -1 slightly worse, 0 no change, 1 slight improvement, 2 much improvement.
Target plaque scores	An individual plaque is scored from 0 (nil) to 4 (very severe) for erythema, scaling and thickness. Total score ranges from 0-12.
Impact	
CDLQI	10 questions, each scored from not at all (0) to very much (3). There are six domains: symptoms and feelings, leisure, school and holidays, personal relationships, sleep and treatment. Total score is out of 30; 0-1 = no effect on child's life, 19-30 = extremely large effect.
DQOLS	17 psychosocial items, grouped into 4 sub-scales (embarrassment, despair, irritability, distress) and 12 physical activities items grouped into 4 sub-scales (everyday activities,

Instrument	Description
	summer, social and sexual). Each uses a 5-point Likert scale (very slightly to extremely) to indicate, "the extent to which you generally feel this way" or "how much your skin problem generally affects or restricts you in these things".
DLQI	10 questions relating to activities in the last week, each scored from not at all (score 0) to very much (score of 3). There are six domains: symptoms and feelings, leisure, school and holidays, personal relationships, sleep and treatment. Total score is out of 30. 0-1 = no effect, 19-30 = extremely large effect.
IPSO	16 items questions, each scored from 1 (none) to 5 (extreme). Covers physical, psychological and social domains.
PDI	15 questions relating to activities in the last 4 weeks. Answers range from not at all (score 0) to very much (score 3). Total score ranges from 0-45.
PSORIQoL	25 item scale covering symptoms and feelings, leisure and personal relationships.
PLSI	15 item questionnaire, each item scored 0-3 on the basis of frequency over the last 4 weeks. Score range 0-45, with >10 indicating significant reaction to stress associated with having psoriasis and <10 not significantly affected by psoriasis related stress.
PQoL-12	Includes 12 items to be rated over the past month using a scale of 0–10; a score of 0–3 represents a low effect, 4–7 represents a medium effect, and 8–10 represents a high effect.
QES	Includes six stigmatization domains: refusal experiences, retreat, self-esteem, rejection, concealment and composure.
Scalpdex	Shortened 23-item version of the Skindex -29 covering symptoms, functioning and emotional domains. The 1 to 5 scale is converted to a score out of 100.
Skindex-29	29 questions for dermatological disease in general covering burden of symptoms, functioning and emotional domains. Items scored on a five-point scale from never to all the time.
Skindex-17	Reduced version of Skindex-29
Dermatology Specific Quality Of Life Instrument	Covers physical symptoms, daily activities, social activities, work/school, experiences, self perception, SF-36, vitality, SF-36 mental subscale.
Severity and impact	
SPI	Comprises 3 domains: PASI (converted into a number from 0-10 for the extent of psoriasis); psychosocial impact of psoriasis on each patient using a 0-10 visual analogue scale; and the historical severity of disease as judged by the need for systemic treatment/admission to hospital/number of episodes of erythroderma. The final score is a three-figure SPI (signs, psychosocial disability and interventions) similar to the TNM staging in cancer (tumour, nodes, metastases).

Thirty five studies were found that addressed the question and were included in this review[51-81 and 82-85].

Few studies reported data regarding the validity and reliability of tools at specific body sites and in different phenotypes of psoriasis:

- Three studies provided data on how well the assessment tools detect site-specific involvement[54,69,71].
- One study addressed assessment of the different phenotypes of psoriasis[54].
- Two studies were solely assessing nail psoriasis[61,62].

No studies were available to assess tools for use in children and although the search of the literature was conducted to cover all levels of healthcare provision no data were available for the reliability and validity of tools in primary care. Additionally, in most studies the stage of the disease journey of the included patients was unclear and a range of disease severities were included.

The study design did not permit meta-analysis or GRADE rating of the data. Therefore, a narrative including summary tables is provided (see 7.4 - 7.10); note that the data in the tables are organised by tool/comparison and by rank order of reliability/validity within that tool/comparison in order to facilitate recognition of variability between the studies. The quality is rated according to domains important for validity and reliability studies (see Appendix Q). Note that study size is not considered in the quality rating but should also be taken into account when assessing the data.

It is important to note that the NICE Technology Appraisals for biologics [7-10] state that one of the necessary criteria that adults with psoriasis must meet before being considered for these treatments is:

- Severe disease is defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
- Very severe disease is defined by a total PASI of 20 or more and a DLQI of more than 18.

Additionally, the NICE Technology Appraisals[7-10] also use PASI and DLQI as measures to assess whether a person with psoriasis has achieved an adequate response, which is defined as either:

- 75% reduction in the PASI score from when treatment started (PASI 75); or

50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.

A summary of the available evidence is provided below, and the data rows in Table 13 - Table 16 are colour-coded and give symbolic representations to represent the tools validity or reliability according to the definitions of adequate, acceptable and poor given in Table 11. It was not possible to categorise the data for the rows that are grey (with the ✍ symbol) owing to the type of data reported.

7.4 Clinical evidence for internal consistency

7.4.1 Evidence summary

Table 13: Summary of included studies assessing internal consistency (ordered by tool and outcome score)

Study	Population	Setting	N	Tool	Internal consistency (Cronbach's α)	
Severity						
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PASI	0.9	👍
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PGA - static	0.9	👍
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	LS-PGA	0.9	👍
Impact						
Shikiar et al (2003)	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	1095	DLQI	0.92 (at end point)	👍

Study	Population	Setting	N	Tool	Internal consistency (Cronbach's α)	
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	DLQI	0.92 (at end point)	👍
McKenna et al (2005)	Psoriasis	Hospital – Secondary/tertiary	72	DLQI	≥0.88	👍
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	DLQI	0.88	👍
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	DLQI	0.92 (at baseline)	👍
Shikiar et al (2003)	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	1095	DLQI	0.87 (at baseline)	👍
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	PSORIQoL	0.94	👍
Gupta and Gupta (1995)	Psoriasis in-patients and out-patients	Secondary/tertiary care	217	PLSI	0.90	👍
Nijsten et al (2005)	Cutaneous psoriasis	Survey of US patients	1196	PDI	Subscales α≥0.77-0.81	👍
Nijsten et al (2006)	Psoriasis (first treated with PUVA)	University centres (USA)	792	IPSO – physical scale	0.85	👍
Nijsten et al (2006)	Psoriasis (first treated with PUVA)	University centres (USA)	792	IPSO – psychological scale	0.73	👍
Nijsten et al (2006)	Psoriasis (first treated with PUVA)	University centres (USA)	792	IPSO – social scale	0.63	☞

7.4.12 Evidence statements for internal consistency

Severity

- There was *adequate* internal consistency (α = 0.9) for PASI, static PGA and LS-PGA [1 study; 35 participants; high quality evidence][60c]

Impact

- There was *adequate* internal consistency for:
  - PSORIQoL (α = 0.94) [1 study; 148 participants; high quality evidence][71]
  - DLQI (α = 0.92-0.87) [4 studies; 1462 participants; high quality evidence][70-72,79]
  - PLSI (α = 0.9) [1 study; 217 participants; high quality evidence][69]
  - IPSO – physical scale (α = 0.85) [1 study; 792 participants; high quality evidence][68]
  - PDI (α = 0.77-0.81 for subscales) [1 study; 1196 participants; high quality evidence][63]

c *Note that this study had a sample size <50*

- IPSO – psychological scale (α = 0.73) [1 study; 792 participants; high quality evidence][68]

- There was *acceptable* internal consistency for the following tool:
  - IPSO – social scale (α = 0.63) [1 study; 792 participants; high quality evidence][68]

7.5 Clinical evidence for test-retest or intra-rater reliability

7.5.1 Evidence summary

Table 14: Summary of included studies assessing test-retest or intra-rater reliability

Study	Population	Setting	N	Tool	Time between tests	Test-retest (intra-rater) reliability	
Severity							
Correlation							
Dommasch et al (2010)	Psoriasis	Secondary/ tertiary care (USA)	22	BSA (number of palms – PREPI method[(a)])	2 days	ICC = 0.99 (0.97-0.99)	👍
Dommasch et al (2010)	Psoriasis	Secondary/ tertiary care (USA)	37	BSA (categorised score – PREPI method[(a)])	2 days	ICC = 0.98 (0.96-0.99)	👍
Ramsay et al (1991)	Chronic plaque psoriasis	In-patients – Secondary/ tertiary care	10	BSA (rule of nines[(b)])	1 day	98-99% agreement*	👍
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PASI	<1 day	ICC = 0.96 (0.93-0.99)	👍
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	PASI	<1 day	ICC = 0.94 (0.86-1.00)	👍
Langley et al (2004)	Psoriasis out-patients	Secondary/ tertiary care (USA)	35	PASI	<1 day	ANOVA $\sigma = 2.5$[(c)]	✍
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary/ care	19	PASI	2 days	r = 0.91*	👍
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	CoPSI	<1 day	ICC = 0.95 (0.92-0.98)	👍
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/ tertiary care (UK)	16	LS-PGA	<1 day	ICC = 0.91 (0.77-1.00)	👍
Langley et al (2004)	Psoriasis out-patients	Secondary/ tertiary care (USA)	35	LS-PGA	<1 day	ANOVA $\sigma = 0.5$[(c)]	✍
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/ tertiary care (UK)	16	PGA – static	<1 day	ICC = 0.88 (0.69-1.00)	👉

Study	Population	Setting	N	Tool	Time between tests	Test-retest (intra-rater) reliability	
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/tertiary care	30	Static PGA (photographs)	1 month (same photograph set)	ICC = 0.84 (95%CI: 0.78-0.90)	
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/ tertiary care	30	Dynamic PGA (photographs)	1 month (same photograph set)	ICC = 0.85 (95%CI: 0.74-0.92)	
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PGA – static	<1 day	ICC=0.81 (0.71-0.90)	
Langley et al (2004)	Psoriasis out-patients	Secondary/ tertiary care (USA)	35	PGA – static	<1 day	ANOVA σ = 0.2[(c)]	
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/ tertiary/ care	19	SAPASI	2 days	r = 0.82*	
Impact							
Correlation							
Kirby et al (2000)	Psoriasis	Secondary/ tertiary care	20	SPI – psychological impact domain only	<1 day	r = 0.997 (95% CI: 0.994-0.999)*	
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	PSORIQoL	2 weeks	ICC=0.89	
Morgan et al. (1997)	Psoriasis (attending phototherapy unit)	Out-patients – Secondary/ tertiary	41	DQOLS	7-10 days	ICC=0.84	
McKenna et al (2005)	Psoriasis	Hospital – Secondary/ tertiary	72	DLQI	2 weeks	r=0.80*	

(a) PREPI: Patient report of extent of psoriasis involvement
(b) Rule of nines: Each of the following body areas are weighted as 9% of the total: head, upper back, chest, right arm, left arm, lower back, abdomen, left upper leg, right upper leg, left lower leg, right lower leg.
(c) σ represents the degree of variability between raters; lower values indicate less variance and so greater reliability
** Note that these are not the most appropriate statistics to assess the outcome*

7.5.2 Evidence statements for test-retest reliability

Severity

There was *adequate* test-retest reliability for the following tools:

- BSA (PREPI method; ICC=0.98-99) [1 study; 22-37 participants; moderate quality evidence][82]*
- PASI (ICC = 0.96-0.94 or r = 0.91) [3 studies; 51 participants; low to high quality evidence][56,59,74]. However, one study also demonstrated a σ of 2.5 from ANOVA for this test, which suggested lower reliability than static PGA and LS-PGA [35 participants; moderate quality evidence][60]

- CoPSI (ICC = 0.95) [1 study; 16 participants; high quality evidence][56]
- LS-PGA (ICC = 0.91) [1 study; 16 participants; high quality evidence][59]. However, one study also demonstrated a σ of 0.5 from ANOVA for this test, which suggested lower reliability than static PGA [35 participants; moderate quality evidence][60]
- BSA (rule of nines; % agreement = 98-99%) [1 study; 10 participants; low quality evidence][67]

There was *acceptable* test-retest reliability for the following tools:

- Static PGA (ICC = 0.81-0.88) [2 studies; 32 participants; high quality evidence][56,59] and static PGA from photographs (ICC = 0.84) [1 study; 30 participants; moderate quality evidence][77]. However, one study also demonstrated a σ of 0.2 from ANOVA for this test, which suggested higher reliability than LS- PGA or PASI [35 participants; moderate quality evidence][60]
- Dynamic PGA (photographs; ICC = 0.85) [1 study; 30 participants; moderate quality evidence][77]
- SAPASI (ICC = 0.82) [1 study; 19 participants; low quality evidence][74]

Impact

There was *adequate* test-retest reliability for the following tools:

- SPI – psychological impact score (r = 0.997) [1 study; 20 participants; moderate quality evidence][81]

There was *acceptable* test-retest reliability for the following tools:

- PSORIQoL (ICC = 0.89) [1 study; 148 participants; very low quality evidence][71]*
- DQOLS (ICC = 0.84) [1 study; 41 participants; very low quality evidence][66]
- DLQI (r = 0.80) [1 study; 72 participants; very low quality evidence][72]*

Note that these were the only studies to have a sample size >50

7.6 Clinical evidence for inter-rater reliability

7.6.1 Evidence summary

Table 15: Summary of included studies assessing inter-rater reliability

Study	Population	Setting	N	Tool	Inter-rater reliability (95% CI)	
Severity						
Correlation						
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary/ care	40	SAPASI[(a)]	ICC=0.953	👍
Fleischer et al (1996)	Psoriasis	Secondary/tertiary care	30	SAPASI[(a)]	97%*	👍
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PASI	ICC = 0.91 (0.84-0.97)	👍
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	PASI	ICC = 0.90 (0.83-0.97)	👍

Study	Population	Setting	N	Tool	Inter-rater reliability (95% CI)	
Faria et al (2010)	Psoriasis	Ambulatory clinic	20	PASI	Assessor 2 vs 3 ICC = 0.817 (0.601-0.923)	
					Assessor 1 vs 2 ICC = 0.729 (0.440-0.882) Assessor 1 vs 3 ICC = 0.753 (0.481-0.894)	
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	20	PASI	r = 0.71 (95% CI: 0.51-0.86)*	
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PASI	ANOVA σ = 8.8[(d)]	
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	20	SPI – historical disease severity domain only[(b)]	r = 0.86 (95% CI: 0.76-0.94)*	
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	LS-PGA	ICC =0.84 (0.73-0.95)	
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	LS-PGA	ANOVA σ = 1.7[(d)]	
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	CoPSI	ICC = 0.83 (0.71-0.95)	
Aktan et al (2007)	Nail psoriasis	Outpatient clinic – Secondary/tertiary care	25	NAPSI	ICC = 0.781 (95% CI: 0.625-0.888)	
Kacar et al (2008)	Nail psoriasis	Secondary/tertiary care	45	NAPSI	r = 0.768*	
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/tertiary care	30	Static PGA (photographs)	ICC = 0.80 (95% CI: 0.68-0.89)	
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	Static PGA	ICC = 0.75 (0.61-0.88)	
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/tertiary care	30	Dynamic PGA (photographs)	ICC = 0.73 (95% CI: 0.56-0.87)	
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	Static PGA	ICC = 0.61 (0.43-0.79)	
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	Static PGA	ANOVA σ = 1.2[(d)]	
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	20	SPI – extent score	r = 0.70 (95% CI: 0.56-0.89)*	

(a) This measurement was based on the agreement between the scores given by 5 raters assessing the body silhouettes of 40 participants, which they had shaded to represent the surface coverage of psoriasis

(b) This domain is judged by the need for systemic treatment, admission to hospital and number of episodes of erythroderma
(c) Rule of nines: Each of the following body areas are weighted as 9% of the total: head, upper back, chest, right arm, left arm, lower back, abdomen, left upper leg, right upper leg, left lower leg, right lower leg.
(d) σ represents the degree of variability between raters; lower values indicate less variance and so greater reliability
** Note that these are not the most appropriate statistics to assess the outcome*

7.6.2 Evidence statements for inter-rater reliability

Severity

There was *adequate* inter-rater reliability for the following tools:

- SAPASI silhouette (ICC = 0.953; or 97% agreement) [2 studies; 70 participants; high quality evidence][65,74]
- SPI – historical disease severity score (r=0.86) [1 study; 20 participants; low quality evidence][81]
- LS-PGA (ICC = 0.84) [1 study; 16 participants; high quality evidence][59]
- CoPSI (ICC = 0.83) [1 study; 16 participants; high quality evidence][56]

There was *acceptable* inter-rater reliability for the following tools:

- Dynamic PGA (photographs; ICC = 0.73) [1 study; 30 participants; moderate quality evidence][77†]
- NAPSI (ICC = 0.768-0.781) [2 studies; 25 participants; moderate quality evidence][61,62]
- Static PGA (ICC =0.61- 0.75) [2 studies; 32 participants; high quality evidence][56,59] and static PGA from photographs (ICC = 0.80) [1 study; 30 participants; moderate quality evidence][77†]
- SPI – extent score (r = 0.70) [1 study; 20 participants; low quality evidence][81]

There was inconsistency between studies in the inter-rater reliability for PASI (ranging from adequate to acceptable):

- It was adequate in 3 studies (ICC = 0.817-0.91) [52 participants; moderate to high quality evidence][56,59,83], but acceptable in 2 studies (ICC = 0.729-0.753) [40 participants; low to moderate quality evidence][81,83].
    - One study [20 participants; low quality evidence][83] found different estimates when comparing different assessors, which ranged from adequate to acceptable, and there was less agreement when disease severity was greatest.

One study [35 participants; moderate quality evidence][60] used the σ value from ANOVA analysis to assess inter-rater reliability. The order of reliability for 3 severity tools was:

- Static PGA>LS-PGA>PASI
- However, after correction for errors in ANOVA the order of reliability changed as listed below, suggesting that the results were very sensitive to variables:
- LS-PGA>static PGA>PASI

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† *This study had a follow-up period of 1 month during which participants were receiving treatment*

7.7 Clinical evidence for construct validity – continuous scales

7.7.1 Evidence summary

Table 16: Summary of included studies assessing construct validity

Study	Population	Setting	N	Tool	Comparison	Construct validity (correlation coefficient)	
CONVERGENT							
Severity							
Iyatomi et al (2009)	Mild psoriasis vulgaris	Secondary/tertiary care	5	PASI	Photographs (computer quantification)	0.922	👍
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	PASI	LS-PGA	0.92	👍
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PASI	LS-PGA	0.86	👍
Henseler and Schmitt-Rau (2008)	Moderate-to-severe chronic plaque psoriasis	Secondary/tertiary care (clinical trial)	33	PASI	SAPASI	0.91	👍
Sampogna et al (2003)	Psoriasis in-patients	Hospital (Italy)– Secondary/tertiary care	351	PASI	SAPASI	0.69	👉
Kirby et al (2001)	Psoriasis in-patients and out-patients	Hospital (UK)– Secondary/tertiary/ care	101	PASI	SAPASI	0.65	👉
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PASI	SAPASI	0.647	👉
Szepietowski et al (2001)	Psoriatic (40 psoriasis vulgaris, 11 PsA)	Unclear	51	PASI	SAPASI	0.62	👉
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary/ care	80	PASI	SAPASI	0.58	👎
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	PASI	SAPASI	0.54	👎
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PASI	CoPSI	0.89	👍
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PASI	Static PGA	0.87	👍
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	PASI	Static PGA	0.83 (at end point)	👍

Study	Population	Setting	N	Tool	Comparison	Construct validity (correlation coefficient)	
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PASI	Static PGA	0.75	
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	PASI	Static PGA	0.79	
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	PASI	Static PGA	0.59 (at baseline)	
Krenzer et al (2011)	Plaque psoriasis	Out-patient and dermatology unit	109	PASI	BSA	0.832 (at 6 months)	
Henseler and Schmitt-Rau (2008)	Moderate-to-severe chronic plaque psoriasis	Secondary/tertiary care (clinical trial)	33	PASI	BSA	0.81	
Krenzer et al (2011)	Plaque psoriasis	Out-patient and dermatology unit	298	PASI	BSA	0.694 (at 3 months)	
Krenzer et al (2011)	Plaque psoriasis	Out-patient and dermatology unit	469	PASI	BSA	0.45 (at baseline)	
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/tertiary care	30	Static PGA (photographs)	Clinical static PGA	0.87 (95% CI: 0.75-0.93)	
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	Static PGA	LS-PGA	0.83	
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	Static PGA	LS-PGA	0.73	
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	Static PGA	CoPSI	0.75	
Henseler and Schmitt-Rau (2008)	Moderate-to-severe chronic plaque psoriasis	Secondary/tertiary care (clinical trial)	33	SAPASI	BSA	0.73	
Szepietowski et al (2001)	Psoriatic (40 psoriasis vulgaris, 11 PsA)	Unclear	51	SAPASI	SPI extent score	0.62	
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	BSA (number of palms)	BSA (PREPI method[(c)] – number of palms)	ICC=0.82 (95% CI: 0.75-0.87)	

Study	Population	Setting	N	Tool	Comparison	Construct validity (correlation coefficient)	
Visit 1							
Dommasch et al (2010) Visit 1	Psoriasis	Secondary/tertiary care (USA)	140	BSA (categorised score)	BSA (PREPI method – categorised score)	ICC = 0.80 (95% CI: 0.73-0.85)	
Dommasch et al (2010) Visit 2 – median 98 days later	Psoriasis	Secondary/tertiary care (USA)	140	BSA (categorised score)	BSA (PREPI method – categorised score)	ICC = 0.71 (95% CI: 0.58-0.80)	
Dommasch et al (2010) Visit 2 – median 98 days later	Psoriasis	Secondary/tertiary care (USA)	140	BSA (number of palms)	BSA (PREPI method – number of palms)	ICC=0.68 (95% CI: 0.54-0.79)	
Fleischer et al (1999)	Psoriasis	Clinical trial – Secondary/tertiary care	182	PASI-equivalent	SAPASI	0.54 (at baseline)	
Fleischer et al (1999)	Psoriasis	Clinical trial – Secondary/tertiary care	182	PASI-equivalent	SAPASI	0.33 (at endpoint)	
Impact							
Nichol et al (1996)	Psoriasis (up to 20% BSA)	Clinical trial (US multicentre)	644	DLQI	PDI	0.82	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	DLQI	PDI	0.805	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	DLQI	IPSO	0.758	
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	DLQI	PSORIQoL	0.70	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	DLQI	PLSI	0.627	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	IPSO	PDI	0.798	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	IPSO	PLSI	0.738	

Study	Population	Setting	N	Tool	Comparison	Construct validity (correlation coefficient)	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PDI	PLSI	0.758	
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	SPI psychological impact score	PDI	0.59	
DIVERGENT							
Severity vs impact							
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PASI	IPSO	0.175	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PASI	DLQI	0.19	
Shikiar et al (2003) Study A	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	498	PASI	DLQI	0.20 (at baseline)	
Shikiar et al (2003) Study B	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	597	PASI	DLQI	0.25 (at baseline)	
Shikiar et al (2003) Study A	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	498	PASI	DLQI	0.51 (at end point)	
Shikiar et al (2003) Study B	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	597	PASI	DLQI	0.59 (at end point)	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PASI	PDI	0.198	
Finlay et al (1990)	Psoriasis in-patients and out-patients	Secondary/tertiary care	32	PASI	PDI	0.40	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PASI	PLSI	0.258	
Kotrulja et al (2010)	50% psoriasis	Hospital – Secondary/tertiary care	140	PASI	PLSI	0.30	
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	PASI	SPI psychological impact score	0.28	
Shankar et al	Psoriasis	Secondary care	34	PASI	PQOL-12	0.42	

Study	Population	Setting	N	Tool	Comparison	Construct validity (correlation coefficient)	
(2011)							
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	PASI	PDI	0.45	👍
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	SAPASI	DLQI	0.261	👍
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	SAPASI	PDI	0.269	👍
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	SAPASI	PDI	0.27	👍
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	SAPASI	IPSO	0.286	👍
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	SAPASI	PLSI	0.354	👍
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	BSA (number of palms)	Skindex-29	0.48 (0.34-0.60)	👍
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	BSA (categorised score)	Skindex-29	0.48 (0.33-0.60)	👍
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	BSA (PREPI method – categorised score)	Skindex-29	0.50 (0.53-0.62)	👍
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	BSA (PREPI method – number of palms)	Skindex-29	0.59 (0.45-0.69)	👍
Kirby et al (2001)	Psoriasis in-patients and out-patients	Hospital (UK)– Secondary/tertiary/ care	101	SAPASI, PASI, SPI	PDI	0.50-0.52	👍

7.712 Evidence statements for construct validity

Convergent construct validity

Comparisons with PASI

There was *adequate* construct validity for the following tools compared with PASI:

- Photographs (computer quantification; r = 0.922) [1 study; 5 participants; very low quality evidence][73†]
- LS-PGA (r = 0.86-0.92) [2 studies; 51 participants; moderate to high quality evidence] [59*60*]
- CoPSI (r = 0.89) [1 study; 16 participants; high quality evidence][56*]

There was inconsistency between and within studies in the construct validity compared with PASI for the following tools:

- SAPASI (r = 0.54-0.91)
  - adequate in 1 study (r = 0.91) [33 participants; low quality evidence][78]*
  - but acceptable in 4 studies (r = 0.62-0.69) [1289 participants; low to high quality evidence][52-54,57]
  - and poor in 2 studies (r = 0.54-0.58) [180 participants; high quality evidence][74,81]
- Static PGA (r = 0.59-0.87)
  - adequate in 3 studies (r = 0.79-0.87) [67 participants; low quality evidence][60]*[56,59]
  - but variable dependent on timing of assessment in 1 intervention study where participants were receiving adalimumab or placebo, being poor at baseline (r = 0.59) but adequate after 12 weeks (r=0.83) [147 participants; low quality evidence][70]
- BSA (r = 0.45-0.832)
  - adequate in 1 study (r = 0.81) [33 participants; moderate to high quality evidence][78]*
  - but variable dependent on timing of assessment in 1 intervention study where participants were receiving efalizumab, being poor at baseline (r = 0.45), acceptable at 3 months (r = 0.694) and adequate at 6 months follow-up (r = 0.832) [469 participants; moderate quality evidence][84]

Comparisons with DLQI

There was *adequate* construct validity for the following tools compared with DLQI:

- PDI (r=0.805-0.82) [2 studies; 1430 participants; moderate quality evidence][53,55]
- IPSO (r=0.758) [1 study; 786 participants; moderate quality evidence][53]
- PSORIQoL (r=0.70) [1 study; 148 participants; low quality evidence][71]

There was *acceptable* construct validity for the following tool compared with DLQI:

- PLSI (r=0.627) [1 study; 786 participants; moderate quality evidence][53]

Comparisons among severity tools (other than PASI)

There was *adequate* construct validity for the following comparisons:

- Static PGA (photographs) vs clinical static PGA (r=0.87) [1 study; 30 participants; low quality evidence][77]*
- CoPSI vs static PGA (r=0.75) [1 study; 16 participants; high quality evidence][56]*
- BSA vs SAPASI (r=0.73) [1 study; 33 participants; low quality evidence][78]*
- Static PGA vs LS-PGA (r=0.73-0.83) [2 studies; 51 participants; moderate to high quality evidence][59]*[60]*

There was *acceptable* construct validity for the following comparisons:

- SAPASI vs SPI extent score (r=0.62) [1 study; 51 participants; low quality evidence][57]

There was *poor* construct validity for the following comparison:

- PASI-equivalent vs SAPASI (r=0.33-0.54) [1 study; 182 participants; high quality evidence][75]

There was inconsistency within one study for the construct validity of BSA as assessed by the patient compared with the physician assessment:

- It was adequate when using the number of palms at visit 1 or categorised score to estimate BSA at visit 1 or visit 2 (median 98 days later) (r=0.71-0.82) but only acceptable when using a the number of palms at visit 2 (r=0.68) [1 study; 140 participants; high quality evidence][82].

Comparisons among impact tools (other than DLQI)

There was *adequate* construct validity for the following comparisons:

- IPSO vs PDI (r=0.798) [1 study; 786 participants; moderate quality evidence][53]
- PDI vs PLSI (r=0.758) [1 study; 786 participants; moderate quality evidence][53]
- IPSO vs PLSI (r=0.738) [1 study; 786 participants; moderate quality evidence][53]

There was *poor* construct validity for the following comparison:

- SPI psychological impact score vs PDI (r=0.59) [1 study; 100 participants; high quality evidence][81]

Divergent construct validity (correlation between severity and impact tools)

There was *adequate* divergent construct validity (suggesting that there are measuring different constructs) for all assessed comparisons (r=0.175-0.59) [8 studies; 2288 participants; low to high quality evidence][53,58,79-81*51,52,82*].

*Note that these studies had a sample size <50

†Note that this study had a sample size <10

7.8 Clinical evidence for construct validity/agreement – dichotomous ratings of response or severity

7.8.1 Evidence summary

Table 17: Summary and rank order of included studies assessing construct validity/agreement

Study	Population	Setting	N	Tool and classification	Comparison	Agreement/ correlation	
CONVERGENT							
Severity							
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary /tertiary care (UK)	16	PASI vs PGA			
				PASI ≤4	PGA clear or nearly clear	K= 0.64 (0.53-0.74)	☞
				PASI ≥18	PGA very severe or severe	K= 0.18 (0.09-0.27)	👎
				PASI vs LS-PGA			
				PASI ≤4	LS-PGA clear or nearly clear	K= 0.61 (0.50-0.73)	☞
				PASI ≥18	LS-PGA very severe or severe	K= 0.62 (0.55-0.69)	☞
				LS-PGA vs PGA			
				LS-PGA clear or nearly clear	PGA clear or nearly clear	K= 0.67 (0.54-0.80)	☞

Study	Population	Setting	N	Tool and classification	Comparison	Agreement/ correlation	
				LS-PGA very severe or severe	PGA very severe or severe	K= 0.08 (0.03-0.14)	
Robinson et al (2012A)	Moderate to severe plaque psoriasis	RCTs for biologics	30 studies	PASI75	PGA clear or nearly clear	8-16 weeks: r = 0.9157 17-24 weeks; r = 0.892 >24 weeks; r = 0.9559	

7.8.12 Evidence statements for construct validity/agreement comparing dichotomous outcomes

Convergent construct validity

There was adequate construct validity between the disease severity outcomes of:

- PASI 75 and clear or nearly clear on PGA at all time points (r=0.891-0.9559) [1 study (summary of 30 RCTs); moderate quality evidence][85]

There was acceptable agreement between the disease severity descriptors of:

- PASI ≤4 and clear or nearly clear on PGA or LS-PGA (K= 0.64 and 0.61, respectively) [1 study; 16 participants; high quality evidence] [59]
- PASI ≥18 and severe or very severe on LS-PGA (K= 0.62) [1 study; 16 participants; high quality evidence] [59]
- Clear or nearly clear on LS-PGA and PGA (K= 0.6) [1 study; 16 participants; high quality evidence] [59]

There was poor agreement between the disease severity descriptors of:

- PASI ≥18 and severe or very severe on PGA (K= 0.18) [1 study; 16 participants; high quality evidence] [59]
- Severe or very severe on LS-PGA and PGA (K= 0.08) [1 study; 16 participants; high quality evidence] [59]

7.9 Clinical evidence for sensitivity to change

7.9.1 Ranking for sensitivity to change (highest to lowest)

Table 18: Summary and rank order of included studies assessing sensitivity to change

Study	Population	Setting	N	Tool	Comparison	Sensitivity to change (correlation coefficient)	
Sensitivity of severity tools to detect clinical change							
Krenzer et al (2011)	Plaque psoriasis	Out-patient and dermatology unit	94	PASI	BSA	0.792 (at 6 months)	
Krenzer et al (2011)	Plaque psoriasis	Out-patient and dermatology	264	PASI	BSA	0.771 (at 3 months)	

Study	Population	Setting	N	Tool	Comparison	Sensitivity to change	
		unit					
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	PASI	Static PGA	0.75	👉
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary/ care	30	PASI	SAPASI	0.63	👉
Fleischer et al (1999)	Psoriasis	Clinical trial – Secondary/tertiary care	182	PASI-equivalent[a]	SAPASI	0.16	👎
Sensitivity of impact tools to detect clinical change							
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	DLQI	Static PGA	0.71	👉
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	DLQI	PASI	0.69	👉
Shikiar et al (2003) Study B	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	597	DLQI	PASI	0.54	👎
Shikiar et al (2003) Study A	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	498	DLQI	PASI	0.47	👎
Shikiar et al (2003) Study B	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	597	DLQI	Dynamic PGA	0.53	👎
Shikiar et al (2003) Study A	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	498	DLQI	Dynamic PGA	0.46	👎

(a) Investigators determined the degree of erythema, induration, scale, body surface area affected, and overall lesion severity of the participants' psoriasis. Using these data, they calculated an investigator PASI-equivalent (erythema + induration + scale, multiplied by percentage body surface area coverage)

7.9.2 Evidence statements for sensitivity to change

Severity tools compared with PASI

There was *acceptable* sensitivity to change for the following tools compared with PASI:

- BSA (r=0.771 after 3 months of treatment to 0.792 after 6 months of treatment) [1 study; 264 participants; low quality evidence][84]
- Static PGA (r=0.75) [1 study; 147 participants; high quality evidence][70]

- SAPASI (r=0.63) [1 study; 30 participants; high quality evidence][74]*

There was *poor* sensitivity to change for the following tool compared with PASI-equivalent:

- SAPASI (r=0.16) [1 study; 182 participants; high quality evidence][75]. Note that this is inconsistent with the result above comparing SAPASI with PASI.

When data were given, a greater percentage reduction in disease severity was reported by PASI than with SAPASI.

Severity tools compared with DLQI

There was inconsistency between the studies for the sensitivity of DLQI to clinical change as measured by different tools to assess severity:

- The DLQI showed *acceptable* sensitivity to detect clinical change as measured by static PGA (r=0.71) [1 study; 147 participants; high quality evidence][70] but *poor* sensitivity to detect clinical change as measured by dynamic PGA (r=0.46-0.53) [2 studies; 1095 participants; high quality evidence][79]
- The DLQI showed *acceptable* sensitivity to detect clinical change as measured by PASI (r=0.69) [1 study; 147 participants; high quality evidence][70] but *poor* sensitivity to change compared with PASI in 2 other studies (r=0.47-0.54) [2 studies; 1095 participants; high quality evidence][79]

**This study had a sample size <50*

Six other studies[63,70,78,79,81,82] reported the sensitivity to change or responsiveness of the tools, but not in terms of a correlation between change scores on two tools. Refer to the summary tables in Appendix Q for details.

7.10 Clinical evidence for practicability

Only 2 studies gave numerical data for the practicability of the tools.

The BSA (PREPI method) showed *adequate* time to administer in clinical practice [1 study; 140 participants; low quality evidence][82].

Photographic PGA showed *acceptable* time to take the photographs in clinical practice (although the time to assess the images is not stated) [1 study; 30 participants; low quality evidence][77].

7.10.1 Ability to detect site-specific severity and impact

7.10.1.1 Severity

There was *acceptable* correlation between the log values of PASI and SAPASI for the following site:

- Trunk [1 study; 351 participants; moderate quality evidence][54]

There was *poor* correlation between the log values of PASI and SAPASI scores for the following sites:

- Head [1 study; 351 participants; moderate quality evidence][54]
- Upper extremities [1 study; 351 participants; moderate quality evidence][54]
- Lower extremities [1 study; 351 participants; moderate quality evidence][54]

The study calculated log values because the distribution was skewed.

7.10.12 Impact

PSORIQoL

In one study [148 participants; low quality][71] PSORIQoL scores were shown to be related to whether or not patients had lesions on their face and/or hands, with *significantly higher* scores among patients with involvement of the hands and/or face.

PLSI

One study [217 participants; low quality][69] showed that there was a *significant correlation* between PLSI scores and self-reported psoriasis severity* for the following body sites (which tended to be associated with greater cosmetic disfigurement):

- Scalp
- Face
- Neck
- Chest
- Right and left arm
- Right and left forearm
- Right and left hand
- Back
- Abdomen

There was *no significant* correlation between PLSI scores and self-reported psoriasis severity* for the following body sites:

- Shoulder
- Hips
- Groin
- Thigh
- Legs
- Feet

**This was measured as a global self-rating of psoriasis severity on a 10-point scale (items: redness, scaling/shedding, plaque thickness, itching and overall severity).*

7.11 Economic Evidence

No relevant economic evidence was identified.

7.12 Recommendations and link to evidence

Recommendations on assessment and referral	**6. Assess people with all types of psoriasis for:** • **disease severity** • **the impact of disease on physical, psychological and social**

	wellbeing • **psoriatic arthritis** • **the presence of comorbidities.** **7. Assess psoriasis severity and impact:** • **at first presentation** • **before referral for specialist advice and at any referral point in the treatment pathway** • **to evaluate the efficacy of interventions.** **8. When assessing the disease severity record:** • **the results of a Static Physician's Global Assessment (PGA) (classified as clear, nearly clear, mild, moderate, severe or very severe)[d]** • **the body surface area (BSA) affected** • **any involvement of nails and high-impact or difficult-to-treat sites (for example, the face, scalp, palms, soles, flexures and genitals)** • **any systemic upset (for example, in people with erythroderma or generalised pustular psoriasis).** **9. In specialist settings, use a validated tool to assess severity, for example the Psoriasis Area and Severity Index (PASI)[e] in adults and for young children use the PGA.** **Be aware that:** • **PASI and BSA are not validated for use in children** • **erythema may be underestimated in people with darker skin types, such as skin types V and VI on the Fitzpatrick scale[f].** **10. Assess the impact of all types of psoriasis on physical, psychological and social wellbeing by asking:** • **what aspects of their daily living are affected by the person's psoriasis** • **how the person is coping with their skin condition and any treatments they are using, and if they need further advice or support** • **if their psoriasis has a big impact on their mood.** **In children and young people also ask about impact on the family and ask age-appropriate questions.**

d See S. R. Feldman and G. G. Krueger. Psoriasis assessment tools in clinical trials. Ann.Rheum.Dis. 64 (Suppl 2):ii65-ii68, 2005.

e See: www.medicareaustralia.gov.au/provider/pbs/drugs1/files/ma_4178_PASI_calculation_and_whole_body_diagram.pdf

f Fitzpatrick scale: type I: always burns, never tans; type II: usually burns, tans with difficulty, type III: sometimes mild burn, gradually tans; type IV: rarely burns, tans with ease; type V: very rarely burns, tans very easily; type VI: never burns, tans very easily

11. In specialist settings and if practical in non-specialist settings, use a validated tool to assess the impact of all types of psoriasis on physical, psychological and social wellbeing, for example the:

- **Dermatology Life Quality Index (DLQI)[g] for adults or**
- **Children's Dermatology Life Quality Index (CDLQI)[h] for children and young people.**

12. Assess whether people with any type of psoriasis are depressed when assessing disease severity and impact, and when escalating therapy. If appropriate offer information, advice and support in line with 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91) for adults and 'Depression in children and young people' (NICE clinical guideline 28) for children and young people.

13. Use the Nail Psoriasis Severity Index[i] to assess nail disease in specialist settings:

- **if there is a major functional or cosmetic impact or**
- **before and after treatment is initiated specifically for nail disease.**

14. Following assessment in a non-specialist setting, offer referral for dermatology specialist advice if:

- **there is diagnostic uncertainty or**
- **psoriasis is severe[j] or extensive, for example more than 10% of BSA involvement or**
- **psoriasis cannot be controlled with topical therapy or**
- **acute guttate psoriasis requires phototherapy or**
- **nail disease has a major functional or cosmetic impact or**
- **any type of psoriasis is having a major impact on a person's physical, psychological or social wellbeing.**

15. People with unstable psoriasis, for example generalised pustular psoriasis or erythroderma, should be referred immediately for same-day specialist assessment and treatment.

16. When using an assessment tool for a person with any type of psoriasis take account their age, any disabilities (such as physical, visual or cognitive impairment), and any language or other communication difficulties, and provide help and support if needed. Ensure that the chosen assessment tool continues to be a sufficiently accurate measure.

g See http://www.dermatology.org.uk/quality/dlqi/quality-dlqi.html
h See http://www.dermatology.org.uk/quality/cdlqi/quality-cdlqi.html
i See Rich P, Scher RK, Nail Psoriasis Severity Index: A useful tool for evaluation of nail psoriasis. JAAD 2003 (49) 206-212.
j Severe as defined on the Static Physician's Global Assessment

	17.Offer specialist referral to children with psoriasis at presentation.
Future research recommendations	**2. What validated tools can be used in people (including children) to assess disease severity and impact in non-specialist and specialist healthcare settings to facilitate assessment, appropriate referral, treatment planning and measurement of outcomes?** **3. What validated tool can be used to assess the impact of disease on physical, psychological and social wellbeing, and how this is influenced by factors including beliefs about psoriasis and distress in non-specialist and specialist healthcare settings?**
Relative values of different outcomes	The outcomes considered by the group were: • construct validity; • internal consistency; • inter-rater / observer reliability; • intra-rater (test-retest) reliability; • practicability; • sensitivity to change. The GDG noted that the relative values of the different outcomes may change, depending on the health care setting and the purpose of using the tool. In primary care or other non-specialist settings, practicability was considered very important; use of complex, time consuming tools requiring training in use and interpretation is unlikely to be feasible, and may not be acceptable to patients. Intra-rater, inter-rater reliability and sensitivity to change were felt to be key outcomes, since accurate and repeatable assessments are crucial for monitoring disease severity and evaluating the impact of treatment over time. These outcomes were given greater value when considering secondary and tertiary care, where disease severity and impact are likely to be greater, and interventions potentially more toxic, and expensive (underlining the need to establish whether or not an intervention is worthwhile). However, there was insufficient data available for sensitivity to change. Divergent construct validity was given priority across all health care settings as this measures whether the tools for assessing severity and impact are measuring different constructs, and therefore whether two tools are needed.
Trade off between clinical benefits and harms	For intra-rater reliability patient assessment of BSA and PASI performed consistently well, with limited evidence also suggesting that LS-PGA and CoPSI may also have good re-test reliability. Static and dynamic PGA appeared to have lower intra-rater reliability. However, the majority of the tests were repeated on the same day, which may have resulted in over-estimation of reliability due to recall bias. There was limited evidence for impact assessment tools on this outcome, but DLQI may have lower re-test reliability than other tools such as SPI psychological domain, PSORIQoL and DQOLS.

The results for inter-rater reliability were variable for PASI, with the correlation ranging from 0.729-0.91. The highest estimates were from the studies with the most raters (14 compared with 3 -6 in other studies) and the lowest estimate was rated as low quality evidence owing to unclear reporting regarding whether the order of raters was randomised or whether they were blinded to the results of other raters and because ICC was not used. There were fewer studies for other tools but the LS-PGA and CoPSI may also have adequate inter-rater reliability, with static and dynamic PGA consistently being reported as less reliable.

The evidence demonstrated that impact and severity tools are measuring different constructs, so it is necessary to assess both impact and severity separately.

In terms of convergent construct validity, all of the moderate to high quality data showed that SAPASI is only moderately well correlated with PASI (r = 0.54-0.69), while more limited data suggested that the CoPSI and LS-PGA demonstrated good correlation with PASI. For both static PGA and BSA there was variation, with generally good correlation, but lower convergence earlier on in intervention studies, suggesting that they may be more convergent in milder disease (i.e. after treatment). For the impact tools, the PDI was the most convergent with DLQI.

One systematic review showed that the outcomes of PASI75 and 0 or 1 on PGA are highly correlated in people with moderate to severe psoriasis treated with biologics.

The GDG agreed that to ensure people with psoriasis had access to appropriate care rapidly and efficiently, holistic assessment in all health care settings and at each stage of the journey was important. Tools for disease assessment have become routine practice in many specialist settings over the last five years, and relevant GDG members felt this had been associated with improved clinical outcomes (e.g. improved awareness of disease impact, ineffective treatments stopped). The GDG noted that in contrast to specialist health care settings, none of the tools had been evaluated in primary care, and that the introduction of validated tools would require time, and training in their use. Nevertheless, the GDG agreed use of tools in primary care would be justified when this is practical and possible. The GDG acknowledged that recommending assessment in primary care would be a big shift in clinical practice. Although there was no evidence for use of tools in primary care, the GDG recommended that disease severity and impact should be assessed in primary care and encourage, but not mandate, the use of formal tools.

In specialist settings, the GDG agreed that the benefits of using formal tools outweighed potential harms, especially since most dermatology specialist settings have health care professionals trained in their use, and that they must be used to meet qualifying disease severity criteria for biologics.

Regarding the data reporting on the comparison of different

	dichotomous definitions of response, in terms of baseline assessments these data indicate that PGA is not useful in more severe disease (if we assume that PASI is the gold standard) but in milder disease a PGA of clear or nearly clear is a reasonable correlate with PASI < 4. However, the GDG noted again that PASI is considered insensitive at the lower end of the disease severity spectrum. When considering treatment response these data support the use of clear or nearly clear when data on PASI 75 is not available and also indicate that PGA correlates adequately with PASI <4 as a 'treatment to target', which is useful in non-specialist settings where PASI may not be an appropriate tool
Economic considerations	No economic evidence was available to inform recommendations about the cost-utility of different psoriasis assessment tools. However, the GDG considered that tools to formally evaluate psoriasis severity and impact would represent a cost-effective improvement to current care. In coming to this conclusion, the GDG considered how a reliable, sensitive and practicable test or combination of tests would help to guide appropriate treatment decisions, measure response to treatment and better identify patients requiring escalation of care. The GDG believes that by using tools to monitor a patient's response to treatment and stopping or changing treatments when they prove ineffective the NHS will ultimately get better value from its resources used.
Quality of evidence	No evidence was found for the use of the tools in children, in primary care settings or for different psoriasis phenotypes. Therefore, all evidence is indirect for these populations. The evidence was largely of moderate to high quality based on assessment of domains relevant for reliability and validity studies. However, there were some studies in which different raters were not blinded to the rating of the others, which may increase the apparent concordance or repeatability of tests (Faria 2008, Finlay 1990, Henseler 2008, Iyatomi 2009) and in others it was unclear if the tests were all conducted by the same raters or whether blinding was in place (Fleischer 1996, Kacar 2008, Kirby 2000, Kotrulja 2010, Krenzer 2011, Robinson 2010, Sampogna 2003 and 2004, Shankar 2011, Szepietowski 2001). Some studies also did not use the most appropriate statistics to summarise their findings, specifically for inter- and intra-rater reliability using continuous data the intra-class correlation coefficient is the ideal statistic, but a number of studies used correlation coefficients or simple agreement (Fleischer 1996, Kacar 2008, Kirby 2000, Feldman 1996, McKenna 2003, Ramsay 1991). A number of studies also had a period of time between the two testing sessions that could have been long enough for changes in the disease severity or impact to have occurred so that any differences in ratings may not reflect a lack of reliability but rather reflect true clinical change over time (it was 2 weeks in the two studies by McKenna [2003 and 2005] and 7-10 days in the study by Morgan et al 1997). Additionally, many of the studies included small numbers of participants.

Other considerations	The GDG agreed that guideline recommendations should align with the existing NICE Technology Appraisals for biologics (Adalimumab for the treatment of psoriasis [TA146]; Etanercept and efalizumab for the treatment of adults with psoriasis [TA103]; Infliximab for the treatment of psoriasis [TA134]; ustekinumab for the treatment of adults with moderate to severe psoriasis [TA180]).[7-10] The technology appraisals state that people with psoriasis who qualify for biologics should be assessed for disease severity using PASI and for disease impact using DLQI. For second-line interventions (non-biological systemics), the tools are not universally routinely used. To qualify for biologics, a patient must have failed these however, and so by inference tools should be used to demonstrate this. The GDG acknowledged that the presence and severity of erythema (also a component of disease severity assessment tools such as PASI) may be underestimated in people with skin type IV and above according to the Fitzpatrick scale[k]. The PASI is for assessment of chronic plaque psoriasis only. A reported 90% of people with psoriasis have chronic plaque psoriasis[1]. There is a need to include tools that capture all types of psoriasis within the recommendations. The GDG chose the BSA to cover all types of psoriasis for all clinical settings. The GDG acknowledged that there were important limitations to this tool: of the prioritised outcomes, only data on sensitivity to change (acceptable) and intra-rater reliability (adequate) are available, some of the studies relate to a patient-assessed rather than a clinician-assessed BSA, and that in practice, estimating body surface area involvement can be difficult especially with small plaque or guttate psoriasis. However, the GDG agreed to recommend it to ensure explicit consideration of the extent of disease. This is important for baseline (See also Glossary) treatment assessment, as those with extensive disease (BSA>10%) are likely to require specialist referral. The BSA was also recommended because it has clinical utility for all types of psoriasis, clinicians would be familiar with the concept of estimating the body surface area involvement and minimal training would be required. The GDG also agreed that a PGA should be performed when assessing disease severity as this would not require significant extra time on top of an assessment of body surface area involvement as both can be estimated at the same time. It was also noted that no formal training would be required for physicians to be able to perform a PGA. Therefore, this should be practical in primary care and, in light of the data on dichotomous ratings of response showing that PGA categories correlate with PASI categories, this tool may provide assessment scores that allow better comparability with PASI for people who are escalated to secondary/tertiary care and so have a PASI assessment at a later point.

[k] Fitzpatrick scale: type I: always burns, never tans; type II: usually burns, tans with difficulty, type III: sometimes mild burn, gradually tans; type IV: rarely burns, tans with ease; type V: very rarely burns, tans very easily; type VI: never burns, tans very easily. See glossary for a more detailed explanation of the Fitzpatrick scale.

	The PASI was chosen for use in specialist settings: this tool performed at least at an adequate level for the prioritised outcomes (intra-rater reliability, inter-rater reliability and sensitivity to change); healthcare professionals in specialist settings are already trained in its use and interpretation; the majority of clinical trials use PASI and therefore treatment effects are quantified using this tool; although the PASI has limitations, there are no other validated tools that are clearly superior at present. It was noted that the BSA is inadequate for assessment of localised pustular psoriasis (acrodermatitis continua of Hallopeau, palmoplantar pustulosis) as it is possible to achieve a low BSA score despite having severe palmoplantar pustulosis, but no evidence was identified for tools that addressed this type of psoriasis. The Nail Psoriasis Severity Index (NAPSI) was chosen for nail disease since BSA and PASI do not assess nail disease. Whilst the GDG have not recommended the Self-administered Psoriasis Area Severity Index (SAPASI), they did discuss its practical issues. It was acknowledged that the Self-administered PASI may be difficult for some people to use because of language or cultural issues, and be inappropriate for people with a learning disability / learning difficulty. In addition to this, from the patient perspective, it can be difficult to self-assess the extent of psoriasis on the back of the body, and assessment tools can be dependent on the person's mood status. The GDG chose the Dermatology Life Quality Index (DLQI) to assess impact of all types of psoriasis because this is a simple, practical tool, that performed at least adequately in the prioritised outcomes, and in the absence of high quality evidence to indicate other tools were better. However, the limitations of the DLQI were acknowledged as significant by the GDG including inadequate capture of the psychological impact of psoriasis. The Skindex-17 may have advantages in this regard but at present there is very limited evidence of its validity and reliability in people with psoriasis. The GDG were aware of ongoing research in this area. On reviewing the evidence, the GDG felt that the ongoing research is warranted as there is a paucity of evidence on validated assessment tools addressing site-specific disease, localised disease (most of the studies were in secondary care and involved severe disease), pustular forms of psoriasis, psoriasis in children, questions about past treatments, and psoriasis involving the skin and joints (combined tools). Beliefs about illness are predictors of distress in other long term conditions and this is not captured in the DLQI. Assessments using these tools should be performed by healthcare professionals who are trained and competent in their use and able to interpret the results.

1

7.13 Assessment and referral for psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory form of arthritis associated with psoriasis and has an estimated incidence rate of 6.6/100,000 per annum[86-89] . In about 80 % of cases the presence of psoriasis precedes the onset of PsA. Whilst there is not a strong correlation between severity of psoriasis and the development of arthritis, PsA may be present more frequently in individuals with psoriasis attending dermatology clinics compared to primary care. There are features that set PsA apart from other forms of inflammatory joint disease including rheumatoid arthritis. Features include the pattern of joint involvement (e.g. distal interphalangeal joint involvement), the swelling of an entire digit (dactylitis), the presence of enthesitis, and the absence of rheumatoid factor (or anti-citrullinated antibodies). Also, an important subgroup of patients with PsA suffer from inflammatory spinal disease (spondylitis) that looks similar but is not identical to ankylosing spondylitis. Other forms of arthritis that may be difficult to distinguish from PsA include osteoarthritis and gout.

The distinction of PsA from other forms of arthritis has been facilitated by the development of the CASPAR classification criteria[90]. The CASPAR criteria have been derived and validated for use in a rheumatology outpatient setting and subsequently shown to work for people with early disease attending a dedicated rheumatology clinic[91] . However non-specialists would not be expected to have the time, knowledge, expertise or resources to differentiate PsA from other conditions that cause musculo-skeletal symptoms using the CASPAR criteria. There are several tools available for use in either primary care or dermatology settings that may help in identifying people with PsA who may benefit from access to rheumatology services.

The GDG agreed to look for evidence relating to the following question: In people with psoriasis (all types), which is the most accurate diagnostic tool to help a non-specialist identify psoriatic arthritis?

7.13.1 Methodological introduction

A literature search was conducted for diagnostic cohorts or case control studies that addressed the accuracy of PsA diagnostic tools designed for use in primary care or by dermatologists, compared with diagnosis by a rheumatologist (using either CASPAR or Moll and Wright criteria, or other specified criteria) in people with psoriasis.

No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The relevant population will not have been previously tested for PsA. The aim of these diagnostic tools is to serve as an initial test for people with psoriasis who also have joint symptoms suggestive of potential PsA. The intended role of an index test would be to indicate likely PsA and therefore prompt subsequent referral to a rheumatologist. A suitable test should be able to accurately rule out a diagnosis other than PsA, so that those with suspected PsA can be referred.

The outcomes considered were:

- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Likelihood ratios (LRs)

The comparisons considered were any of the following diagnostic tools compared with the Classification Criteria for Psoriatic Arthritis (CASPAR), the Moll and Wright criteria or standard clinical diagnosis:

- Psoriatic Arthritis Screening and Evaluation Tool (PASE)

- Psoriasis Epidemiology Screening Tool (PEST)
- Toronto Psoriatic Arthritis Screen (ToPAS)
- Psoriatic Arthritis Questionnaire (PAQ)
- Modified PAQ (mPAQ)

Only one of the studies used a formal diagnostic tool as the reference standard, which was the Moll and Wright criteria[92]. However, the stated protocols in the other studies were similar to the Moll and Wright or CASPAR criteria.

It was not possible to analyse the data using meta-analysis or the standard version of GRADE. A modified version of GRADE has been used and a narrative summary is provided. The statistics used for this diagnostic review differ from those used in intervention reviews, and a definition for each of them is provided in Table 19 below. Although no meta-analysis has been performed, forest plots are provided as a visual aid presenting the sensitivity and specificity of the tools compared with clinical diagnosis as reported in the studies individually (Appendix J).

Table 19: Definitions of summary statistics for diagnostic accuracy studies

Measure	Definition
True positives (TP)	Correct positive test result – number of people with PsA with a positive index test result
True negatives (TN)	Correct negative test results – number of people without PsA with a negative index test result
False positives (FP)	Incorrect positive test result – number of people without PsA with a positive index test result
False negatives (FN)	Incorrect negative test result – number of people with PsA with a negative index test result
Sensitivity	Proportion of those *with* the disease (based on reference standard) who are *positive* on the index test
Specificity	Proportion of those *without* the disease (based on reference standard) who are *negative* on the index test
Positive predictive value (PPV)	Probability of having the disease in a patient with a *positive* index test result
Negative predictive value (NPV)	Probability of not having the disease in a patient with a *negative* index test result
Positive likelihood ratio (LR+)	The number of times more likely a positive test result is in a person with compared to a person without the disease (therefore LR- is >1)
Negative likelihood ratio (LR-)	The number of times more likely a negative test result is in a person with compared to a person without the disease (therefore LR- is <1)

Positive and negative predicative values are dependent on disease prevalence (pre-test probability) and so need to be interpreted together with prevalence, in the context of how test results modify the probability of disease (post-test probabilities). The lower the prevalence of disease the more certain we can be that a negative test indicates no disease, and the less certain that a positive result truly indicates the presence of disease. A note on how to interpret post-test probabilities/predictive values in the light of the disease prevalence is provided in Appendix Q.

A summary of the included index tests is provided in Table 20.

Table 20: Description of index tests being assessed for diagnostic accuracy

Test	Setting developed in	Description
Psoriatic Arthritis Screening and Evaluation Tool (PASE)	Dermatology-rheumatology clinic	Developed specifically to help dermatologists identify individuals with psoriasis who need prompt referral to rheumatology. 15-item questionnaire divided into 2 subscales (7 symptoms questions and 8 function questions). Initial question pool derived from literature review, patient data and interviews and expert consensus of dermatologists and rheumatologists using the Delphi process.
Psoriasis Epidemiology Screening Tool (PEST)	Community setting and hospital clinic	Based on the PAQ and modified PAQ with additional questions relating to spondyloarthropathy and dactylitis.
Toronto Psoriatic Screening Tool (ToPAS)	Dermatology-rheumatology clinic	Designed for use in patients both with and without psoriasis. 12-item questionnaire, including pictures of psoriatic skin and nail lesions, along with questions about pain and stiffness in the joints and back. Questions were generated following a review of items by PsA patients and question selection was performed by rheumatologists and dermatologists. Questions were also reviewed by patients for readability and investigators for face validity.
Psoriatic Arthritis Questionnaire (PAQ)	Dermatology clinic	Designed to detect arthritis among patients with psoriasis. 11-item questionnaire (1 question removed from the original 12-item form – 'has a doctor ever told you that you have arthritis?' – to make it applicable to a population not knowing whether they have arthritic disease). Range: 0-8
Weighted modification of PAQ (mPAQ)	Community setting and hospital clinic	Questions that were found to most strongly predict arthritis were given a double score compared with the other questions. Range: 0-9

Five diagnostic studies were found that addressed the question and were included in the review[92-96]. Note that there were no data available for the use of these tools in children with psoriasis and suspected psoriatic arthritis.

These studies differed in terms of:

- Mean age (range >18 to 55 years)
- Gender: % male (range 49 to 62%)
- Sample size (range N=69 to N=257)

Quality assessment (QUADAS 2 criteria)[97] of the included studies showed that they:

- Had variable selection criteria of participants: some included patients who already had a known diagnosis of PsA (not applicable to a screening population)[92,94,95] and one excluded difficult to diagnose patients[96]
- Had reporting bias: all studies lacked clarity of reporting, particularly for patient flow (including whether all patients received both tests and/or were included in the analysis and the time interval between the tests)
- Largely avoided verification bias (i.e. all patients in the studies received the same comparison tests, regardless of initial results)
- All had an unclear period of time between the index test and reference standard
- All had either unclear[95] or post-hoc[92-94,96] selection of threshold values. Therefore, they are likely to have been chosen to optimise sensitivity and specificity, which could lead to over-optimistic measures of test performance (although as these were initial validation studies this may be reasonable)
- All had unclear evidence of blinding to previous results

7.13.2 Study details – methods and results

The study methods are graded in the evidence profile (Table 21) and a summary of the study results is provided in Table 22. In the narrative below, methodological flaws according to the QUADAS-II criteria are noted as points to suggest caution when interpreting results.

7.13.2.1 ToPAS

Methods

One study[94] was found that investigated the diagnostic accuracy of ToPAS in people with psoriasis. The reference standard was clinical diagnosis by trained rheumatologists according to a standard protocol including a complete history, physical examination, routine laboratory tests, rheumatoid factor and anti-nuclear factor. Radiographs were performed in all patients with known PsA but were only performed if there was a clinical suspicion of arthritis in other patients (i.e., joint or back pain or limitation of movement, or joint deformities). A diagnosis of PsA was made if there was inflammatory arthritis in the presence of psoriasis.

The results of this study should be interpreted with caution as the sample included 52% of people with known PsA. This does not match the specified population and would be likely to increase the apparent sensitivity of the test.

Results

Sensitivity and specificity: This study found that using a threshold for diagnosis of ≥8 ToPAS had a sensitivity of 89%, meaning that a negative result may be useful for ruling out a diagnosis of PsA (89% of patients with PsA would be expected to test positive on this questionnaire); the ToPAS had a specificity of 86%, suggesting that a positive result may also be useful for ruling in disease (86% of patients without PsA would be expected to test negative on this questionnaire).

Positive predictive value/negative predictive value: If the ToPAS was positive the probability of having PsA (PPV) was 91.8% and if the ToPAS was negative the probability of *not* having PsA (NPV) was 81.6% (18.4% chance of having PsA despite having a negative test).

Given that the pre-test probability of having PsA was 64%, this means that the ToPAS questionnaire improves the ability to determine a positive diagnosis (over and above the known prevalence) by

27.8%; and a negative diagnosis by 45.6%. However, the accuracy of the ToPAS may not be sufficient to either confirm or exclude PsA.

Likelihood ratio: A positive test result is 6.37 times more likely in a person with compared to a person without PsA, and a negative test result is 7.69 times more likely in a person without compared to a person with PsA; again this suggests that the test is slightly better at ruling out than ruling in a diagnosis.

7.13.272 PASE

Methods

There were two studies[92,96] that investigated the diagnostic accuracy of PASE in people with psoriasis. In both studies the reference standard was clinical diagnosis on the basis of joint exam (including presence of dactylitis and/or synovitis and/or nail pitting), clinical history including history of morning stiffness and radiographs based on Moll and Wright Criteria plus evaluation by a rheumatologist. The studies differed in sample size (69 and 190) and optimal threshold score for sensitivity and specificity (≥47 and ≥44). One study also presented the accuracy of the test in a population that excluded those with quiescent or asymptomatic disease (based on rheumatological evaluation), but those excluded were still considered to have PsA based on their evaluation[92].

The results of the Husni study [96]should be interpreted with caution as the sample excluded difficult to diagnose patients (i.e., when there was disagreement between the rheumatologists regarding the final diagnosis), and this may result in bias.

Results

Sensitivity and specificity: The findings for the sensitivity and specificity of PASE varied between the studies. Based on the threshold of ≥47 PASE had a sensitivity of 70-82 and specificity of 73-80%. Based on the lower threshold of ≥44 in one study[92], PASE had a sensitivity of 76% and specificity of 76%. Therefore, PASE may be useful for suggesting a diagnosis of PsA in the absence of a better screening tool for psoriasis patients.

As expected, assessing the subset of patients that excluded quiescent or asymptomatic disease (using the threshold of ≥47) gave a higher sensitivity (93%), but similar specificity (80%). This suggests that PASE is not able to detect PsA that is quiescent or asymptomatic.

Positive predictive value/negative predictive value: If the PASE was positive the probability of having PsA (PPV or proportion of patients with a positive test who are correctly diagnosed) ranged from 43.1 to 50.0% and if the PASE was negative the probability of *not* having PsA (NPV or proportion of patients with a negative test who are correctly diagnosed) ranged from 91.7 to 92.8% (7.2 to 8.3% chance of having PsA despite having a negative test).

Given that the pre-test probabilities of having PsA were 25% and 19.5% in the two studies, this means that the PASE questionnaire improves the ability to determine a positive diagnosis (over and above the known prevalence) by 23.6 to 26.1%; and a negative diagnosis by 11.2 to 17.7%. This implies that PASE is not useful for confirming or excluding a diagnosis of PsA.

Even considering the population that excluded quiescent or asymptomatic disease the PPV remained low (44.6%), although the NPV was improved (98.4%). Given that the pre-test probability of having PsA was 15%, this means that the PASE questionnaire improves the ability to determine a positive diagnosis in a sample of patients with active PsA (over and above the known prevalence) by 29.6% and a negative diagnosis by 13.4%

Likelihood ratio: A positive test result ranges from 3.06 to 3.47 times more likely in a person with compared to a person without PsA, and a negative test result ranges from 2.70 to 4.17 times more likely in a person without compared to a person with PsA. These ratios were improved by considering the population excluding quiescent or asymptomatic disease, which gave a positive test result as being 4.57 times more likely in a person with compared to a person without PsA, and a negative test result being 11.1 times more likely in a person without compared to a person with PsA.

Additional information

- Two studies[92,96] demonstrated that the PASE scores were higher in people with PsA than in people with osteoarthritis:
  - Husni study: symptom and function scores: p=0.01; total score: p=0.007
  - Dominguez study: symptom score: p=0.014; function score: p=0.082 (NS); total score: p=0.039
- One study[96] demonstrated that the PASE scores were higher in people with severe PsA than in people with non-severe PsA:
  - Symptom score: p=0.02; function score: p=0.051 (NS); total score: p=0.02
- One study[92] reported characteristics of the false positive and false negative participants:
  - Of nine false negatives, four had limited disease, two had quiescent disease, one had axial involvement, one participant received multiple intra-articular injections 10 days prior to PASE administration and another participant had been off non-biological systemic therapy for 5 months but began flaring at the time of PASE administration.
  - Of 37 false positives, 18 had a history of other musculoskeletal conditions (e.g., severe osteoarthritis/degenerative joint disease, spinal stenosis, carpal tunnel syndrome, chondromalacia, muscle strain, and muscle sprain), seven participants had undifferentiated arthritis, four had gout, two had fibromyalgia, one had peripheral neuropathy, one had spondyloarthropathy and one had lupus. The medical records of the three remaining individuals were unavailable.

7.13.263 PAQ

Methods

There were two studies[93,95] that investigated the diagnostic accuracy of PAQ (as modified by Alenius) in people with psoriasis. In both studies the reference standard was diagnosis on the basis of clinical examination and history by a rheumatologist. The studies differed in sample size (N=202 and N=114) but used the same threshold score for sensitivity and specificity (≥4). One study assessed results for two different diagnoses: peripheral arthritis and/or axial disease; and any inflammatory manifestation, including peripheral arthritis, axial disease, undifferentiated spondyloarthritis and peripheral enthesitis/tenosynovitis. These two samples overlap, but the second may be more relevant as enthesitis can be an important component of PsA and is also part of the CASPAR criteria.

The results of one study[95] may have been biased owing to the sample including 18.4% of people with known PsA, which does not match the specified population and would be likely to increase the apparent sensitivity of the test. Additionally, not all of the participants were analysed in the calculations but the reasons for drop-out are unclear.

Results

Sensitivity and specificity: The findings for the sensitivity and specificity of PAQ varied between the studies, but were low in all cases. Based on the threshold of ≥4 PAQ had a sensitivity ranging from 55 to 63% and specificity from 62 to 72%. Therefore, PAQ may not be useful for suggesting a diagnosis of PsA in psoriasis patients. Note that in the Alenius study the sensitivity was lowest for detecting any

inflammatory manifestation, but the specificity was lowest for detecting peripheral arthritis and/or axial disease.

Positive predictive value/negative predictive value: Similarly, the PPV and NPV suggest poor performance of the PAQ in this population. If the PAQ was positive the probability of having PsA (PPV or proportion of patients with a positive test who are correctly diagnosed) ranged from 26.1 to 48.8% and if the PAQ was negative the probability of not having PsA (NPV or proportion of patients with a negative test who are correctly diagnosed) ranged from 71.9 to 87.5% (12.5 to 28.1% chance of having PsA despite having a negative test).

Given that the pre-test probabilities of having PsA were 18.2, 36.4 and 29.6% in the three populations, this means that the PAQ questionnaire improves the ability to determine a positive diagnosis (over and above the known prevalence) by 7.9 to 19.2% and a negative diagnosis by 5.7 to 11.7%. This implies that PAQ is not useful for confirming or excluding a diagnosis of PsA. Note that in the Alenius study the PPV was lowest for detecting peripheral arthritis and/or axial disease, but the NPV was lowest for detecting any inflammatory manifestation.

Likelihood ratio: A positive test result ranges from 1.59 to 2.26 times more likely in a person with compared to a person without PsA, and a negative test result ranges from 1.47 to 1.92 times more likely in a person without compared to a person with PsA. Note that in the Alenius study the likelihood ratios were similar for detecting either peripheral arthritis and/or axial disease or any inflammatory manifestation.

7.13.2.4 mPAQ

Methods

One study[93] investigated the diagnostic accuracy of a further modified version of PAQ (with scores on the questionnaire weighted according to their ability to predict arthritis) in people with psoriasis. The reference standard was diagnosis on the basis of clinical examination and history by a rheumatologist.

Results

Even when the scores on the PAQ questionnaire were weighted according to their ability to predict arthritis the test still had poor diagnostic accuracy[93].

Sensitivity and specificity: The findings for the sensitivity and specificity of mPAQ based on the threshold of ≥5 PAQ were poor, showing a sensitivity of 50% for peripheral or axial disease and 45% for any inflammatory manifestation; while the specificities were 73 and 77%, respectively.

Positive predictive value/negative predictive value: Again, the PPV and NPV suggested poor performance of the mPAQ in this population. If the mPAQ was positive the probability of having PsA (PPV or proportion of patients with a positive test who are correctly diagnosed) were 29.4% for peripheral or axial disease and 52.9% for any inflammatory manifestation; and if the PAQ was negative the probability of *not* having PsA (NPV or proportion of patients with a negative test who are correctly diagnosed) was 86.8% for peripheral or axial disease and 71.1% for any inflammatory manifestation (13.2 and 28.9% chance of having PsA despite having a negative test, respectively).

Given that the pre-test probabilities of having PsA were 18.2 and 36.4% in the two populations, this means that the mPAQ questionnaire improves the ability to determine a positive diagnosis (over and above the known prevalence) by 11.2 and 16.5% and a negative diagnosis by 5.0 and 7.5% for peripheral or axial disease and any inflammatory manifestation, respectively. This implies that mPAQ is not useful for confirming or excluding a diagnosis of PsA.

Likelihood ratio: A positive test result was 1.88 and 1.97 times more likely in a person with compared to a person without peripheral or axial disease and any inflammatory manifestation, respectively; and a negative test result ranges from 1.47 and 1.41 times more likely in a person without compared to a person with peripheral or axial disease and any inflammatory manifestation, respectively.

7.13.2.5 PEST

Methods

There was one study[95] that investigated the diagnostic accuracy of PEST in people with psoriasis. The reference standard was diagnosis on the basis of clinical examination and history by a rheumatologist.

The results of this study should be interpreted with caution because they may have been biased owing to the sample including 18.4% of people with known PsA, which does not match the specified population and would be likely to increase the apparent sensitivity of the test.

Results

Sensitivity and specificity: This study found that using a threshold for diagnosis of ≥3 PEST had a sensitivity of 91%, meaning that a negative test result may be useful for ruling out a diagnosis of PsA (91% of patients with PsA would be expected to test positive on this questionnaire); the PEST had a specificity of 77% (77% of patients without PsA would be expected to test negative on this questionnaire).

Positive predictive value/negative predictive value: If the PEST was positive the probability of having PsA (PPV) was 61.2% and if the PEST was negative the probability of *not* having PsA (NPV) was 95.4% (4.6% chance of having PsA despite having a negative test).

Given that the pre-test probability of having PsA was 28.9%, this means that the PEST questionnaire improves the ability to determine a positive diagnosis (over and above the known prevalence) by 32.3% and a negative diagnosis by 24.3%. This implies that its accuracy may not be sufficient to either confirm or exclude PsA.

Likelihood ratio: A positive test result is 3.88 times more likely in a person with compared to a person without PsA, and a negative test result is 8.33 times more likely in a person without compared to a person with PsA; this suggests that the test is better at ruling out than ruling in a diagnosis.

7.13.3 Evidence profile

Table 21: Modified GRADE profile for the diagnostic accuracy of tools to detect PsA

Study characteristics			Quality Assessment					Summary of findings					
No. of studies	**Design**	**No. of patients**	**Limitation**	**Inconsistency**	**Indirectness**	**Imprecision***	**Other consideration**	**Pre-test probability**	**Sensitivity**	**Specificity**	**Post-test probability positive (if positive result)**	**Post-test probability negative (if negative result)**	**Quality**
ToPAS vs clinical diagnosis													
1 Gladman 2009	Diagnostic cohort	257	VS[a]	N	S[b]	N	TH ≥8	0.64	89.1 (83-93.2)%	86.3 (76.4-92.5)%	91.8 (87.9-94.8)%	81.6 (75.2-86.5)%	⊕OOO VERY LOW
PASE vs clinical diagnosis													
1 Husni 2007	Diagnostic cohort	69	VS[c]	N	N	S*	TH ≥47	0.25	82.4 (57-96)%	73.1 (59-84)%	50.0 (36.0-57.8)%	92.7 (83.1-98.0)%	⊕OOO VERY LOW
1 Dominguez 2009	Diagnostic cohort (Using Moll and Wright criteria)	190	VS[d]	N	N[e]	S*	TH ≥47	0.195	70 (53-84)%	80 (73-86)%	45.6 (35.7-53.6)%	91.7 (87.5-95.2)%	⊕OOO VERY LOW
		180[#]	VS[d]	N	N[e]	N	TH ≥47	0.15	93 (78-99)%	80 (73-86)%	44.6 %	98.4%	⊕⊕OO LOW
		190	VS[d]	N	N[e]	N	TH ≥44	0.195	76 (59-88)%	76 (68-82)%	43.1 (34.4-49.6)%	92.8 (88.3-96.2)%	LOW
PAQ vs clinical diagnosis													
1	Diagnostic	165	VS[f]	N	N	S*	TH ≥4	A: 0.182	A: 60 (41-	A: 62.2 (53-	A: 26.1 (18.4-	A: 87.5	⊕OOO

Study characteristics			Quality Assessment					Summary of findings					
No. of studies	**Design**	**No. of patients**	**Limitation**	**Inconsistency**	**Indirectness**	**Imprecision***	**Other consideration**	**Pre-test probability**	**Sensitivity**	**Specificity**	**Post-test probability positive (if positive result)**	**Post-test probability negative (if negative result)**	**Quality**
Alenius 2002	cohort							B: 0.364	77)% B: 55 (42-86)%	70)% B: 65.7 (56-75)%	32.9)% B: 47.8 (38.4-56.7)%	(82.0-92.4)% B: 71.9 (65.1-78.3)%	VERY LOW
1 Ibrahim 2009	Diagnostic cohort/case control	114	VS[g]	N	S[h]	S*	TH≥4	0.296	63 (44-79)%	72 (61-82)%	48.8 (36.4-59.6)%	82.1 (74.5-88.7)%	⊕OOO VERY LOW
mPAQ vs clinical diagnosis													
1 Alenius 2002	Diagnostic cohort	165	VS[f]	N	N	S*	TH ≥5	A*: 0.182 B**: 0.364	A: 50 (31-69)% B: 45 (32-58)%	A: 73.3 (65-81)% B: 77.1 (68-85)%	A: 29.4 (19.5-39.2)% B: 52.9 (40.9-64.4)%	A: 86.8 (82.4-91.2)% B: 71.1 (65.7-76.2)%	⊕OOO VERY LOW
PEST vs clinical diagnosis													
1 Ibrahim 2009	Diagnostic cohort/case control	114	VS[g]	N	S[h]	S*	TH≥3	0.289	91 (76-98)%	77 (66-85)%	61.2 (51.9-65.7)%	95.4 (88.3-98.8)%	⊕OOO VERY LOW

**Imprecision is assessed based on the sensitivity, specificity PPV and NPV of the tests; if there was no majority in the assessment of imprecision across these statistics higher weighting was given to sensitivity and NPV as these are most important for the intended role of the test.*

VS = very serious; S = serious; N = no serious; TH = threshold

(a) Unclear if reference standard was assessed blinded to index test results/index test analysed blinded to reference standard results; post-hoc selection of threshold; time between tests unclear

(b) Some patients already had a known diagnosis of PsA (not applicable to a screening population)

(c) Unclear if patient selection method is appropriate; difficult to diagnose patients excluded; unclear if reference standard was assessed blinded to index test results/index test analysed blinded to reference standard results; post-hoc selection of threshold; time between tests unclear

(d) Unclear if patient selection method is appropriate; unclear if reference standard was assessed blinded to index test results/index test analysed blinded to reference standard results; post-hoc selection of threshold; time between tests unclear

(e) PsA diagnosis new in the majority of participants and if not no treatment for PsA received

(f) Unclear if reference standard was assessed blinded to index test results/index test analysed blinded to reference standard results; post-hoc selection of threshold; time between tests unclear; 22.8% dropped out

(g) Unclear if reference standard was assessed blinded to index test results/index test analysed blinded to reference standard results; unclear method of selection of threshold; time between tests unclear

(h) Separate series of known PsA cases also completed the questionnaire (introduces case-control bias)

A: Peripheral arthritis and/or axial disease

B: Any inflammatory manifestation

[#]This was the sample population excluding those with quiescent or asymptomatic disease

7.13.4 Evidence Summary

Table 22: Summary statistics for diagnostic accuracy of tools for PsA

Study	N	Threshold	Pre-test probability	Sensitivity	Specificity	PPV Value-added PPV	NPV Value-added NPV	Post-test probability of PsA despite test –ve (1 – NPV)	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
ToPAS vs clinical diagnosis										
Gladman 2009	257	≥8	64%	89.1 (83-93.2)%	86.3 (76.4-92.5)%	91.8 (87.9-94.8)% *27.8%*	81.6 (75.2-86.5)% *45.6%*	18.4%	6.37 (3.84-11.0)	0.13 (0.08-0.20)
PASE vs clinical diagnosis										
Husni 2007	69	≥47	25%	82.4 (57-96)%	73.1 (59-84)%	50.0 (36.0-57.8)% *25.0%*	92.7 (83.1-98.0)% *17.7%*	7.3%	3.06 (1.86-5.04)	0.24 (0.09-0.68)
Dominguez 2009	190	≥44	19.5%	76 (59-88)%	76 (68-82)%	43.1 (34.4-49.6)% *23.6%*	92.8 (88.3-96.2)% *12.3%*	7.2%	3.13 (2.24-4.37)	0.32 (0.18-0.57)
		≥47	19.5%	70 (53-84)%	80 (73-86)%	45.6 (35.7-53.6)% *26.1%*	91.7 (87.5-95.2)% *11.2%*	8.3%	3.47 (2.38-5.06)	0.37 (0.23-0.62)
	180 #	≥47	15%	93 (78-99)%	80 (73-86)%	44.6 % *29.6%*	98.4% *13.4%*	1.6%	4.57	0.09
PAQ vs clinical diagnosis										
Ibrahim 2009	114	≥4	29.6	63 (44-79)%	72 (61-82)%	48.8 (36.4-59.6)% *18.8%*	82.1 (74.5-88.7)% *11.8%*	17.9%	2.26 (1.44-3.55)	0.52 (0.32-0.83)
Alenius 2002	165	≥4	A: 18.2% B: 36.4%	A: 60 (41-77)% B: 55 (42-86)%	A: 62.2 (53-70)% B: 65.7 (56-75)%	A: 26.1 (18.4-32.9)% *A: 7.9%* B: 47.8 (38.4-56.7)% *B: 11.4%*	A: 87.5 (82.0-92.4)% *A: 5.7%* B: 71.9 (65.1-78.3)% *B: 8.3%*	A: 12.5% B: 28.1%	A: 1.59 (1.10-2.28) B: 1.60 (1.13-	A: 0.64 (0.41-1.02) B: 0.68 (0.50-

Study	N	Threshold	Pre-test probability	Sensitivity	Specificity	PPV Value-added PPV	NPV Value-added NPV	Post-test probability of PsA despite test –ve (1 – NPV)	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
									2.28)	0.94)
mPAQ vs clinical diagnosis										
Alenius 2002	165	≥5	A: 18.2% B: 36.4%	A: 50 (31-69)% B: 45 (32-58)%	A: 73.3 (65-81)% B: 77.1 (68-85)%	A: 29.4 (19.5-39.2)% *A: 11.2%* B: 52.9 (40.9-64.4)% *B: 16.5%*	A: 86.8 (82.4-91.2)% *A: 5.0%* B: 71.1 (65.7-76.2)% *B: 7.5%*	A: 13.2% B: 28.9%	A: 1.88 (1.19-2.95) B: 1.97 (1.26-3.08)	A: 0.68 (0.47-0.99) B: 0.71 (0.55-0.92)
PEST vs clinical diagnosis										
Ibrahim 2009	114	≥3	28.9%	91 (76-98)%	77 (66-85)%	61.2 (51.9-65.7)% *33.6%*	95.4 (88.3-98.8)% *24.4%*	4.6%	3.88 (2.58-5.83)	0.12 (0.04-0.35)

NPV: Negative predictive value
PPV: Positive predictive value
A: Peripheral arthritis and/or axial disease
B: Any inflammatory manifestation
[#]This was the sample population excluding those with quiescent or asymptomatic disease

7.13.15 Evidence statements

The following statements are organised by outcome and list the tests in order from the best to the worst diagnostic accuracy.

- **Sensitivity** was highest for PEST and ToPAS (as well as PASE in active disease), but all of these studies included some patients with known PsA
  - PASE (active disease): 93% [1 study; 180 participants; low quality evidence][92]
  - PEST: 91% [1 study; 114 participants; very low quality evidence][95]
  - ToPAS: 89.1% [1 study; 257 participants; very low quality evidence][94]
  - PASE: 70-82.4% [2 studies; 159 participants; low to very low quality evidence][92,96]
  - PAQ: 55-63% [2 studies; 279 participants; very low quality evidence][93,95]
  - mPAQ: 45-50% [1 study; 165 participants; very low quality evidence][93]
- **Specificity** was best for ToPAS, followed by PEST and PASE
  - ToPAS: 86.3% [1 study; 257 participants; very low quality evidence][94]
  - PASE (active disease): 80% [1 study; 180 participants; low quality evidence][92]
  - PEST: 77% [1 study; 114 participants; very low quality evidence][95]
  - PASE: 73.1-80% [2 studies; 159 participants; low to very low quality evidence][92,96]
  - mPAQ: 73.3-77.1% [1 study; 165 participants; very low quality evidence][93]
  - PAQ: 62.2-72% [2 studies; 279 participants; very low quality evidence][93,95]
- The **positive predictive value** was best for ToPAS and the **negative predictive value** for PASE and PEST (this section is ordered according to the best negative predictive value)
  - PASE (active disease): PPV 44.6%; NPV 98.4% [1 study; 180 participants; low quality evidence][92]
  - PEST: PPV 61.2%; NPV 95.4% [1 study; 114 participants; very low quality evidence][95]
  - PASE: PPV 43.1-50.0%; NPV 91.7-92.8% [2 studies; 159 participants; low to very low quality evidence][92,96]
  - ToPAS: PPV 91.8%; NPV 81.6% [1 study; 257 participants; very low quality evidence][94]
  - PAQ: PPV 26.1-48.8%; NPV 71.9-87.5% [2 studies; 279 participants; very low quality evidence][93,95]
  - mPAQ: PPV 29.4-52.9%; NPV 71.1-86.8% [1 study; 165 participants; very low quality evidence][93]
- The **post test probability of PsA modified by prevalence** was most improved in PEST, followed ToPAS and PASE, for a positive result and ToPAS for a negative result (this section is ordered according to the best negative predictive value)
  - ToPAS: positive 27.8%; negative 45.6% [1 study; 257 participants; very low quality evidence][94]
  - PEST: positive 32.3%; negative 24.3% [1 study; 114 participants; very low quality evidence][95]
  - PASE: positive 23.6-25.0%; negative 11.2-17.7% [2 studies; 159 participants; low to very low quality evidence][92,96]
  - PASE (active disease): positive 29.6%; negative 13.4% [1 study; 180 participants; low quality evidence][92]
  - PAQ: positive 7.9-19.2%; negative 5.7-11.7% [2 studies; 279 participants; very low quality evidence][93,95]
  - mPAQ: positive 11.2-16.5%; negative 5.0-7.5% [1 study; 165 participants; very low quality evidence][93]

- The **positive likelihood ratio** was best for ToPAS, followed by PEST and PASE
  - ToPAS: 6.37 [1 study; 257 participants; very low quality evidence][94]
  - PASE (active disease): 4.57 [1 study; 180 participants; low quality evidence][92]
  - PEST: 3.88 [1 study; 114 participants; very low quality evidence][95]
  - PASE: 3.06-3.47 [2 studies; 159 participants; low to very low quality evidence][92,96]
  - PAQ: 1.59-2.26 [2 studies; 279 participants; very low quality evidence][93,95]
  - mPAQ: 1.88-1.97 [1 study; 165 participants; very low quality evidence][93]
- The **negative likelihood ratio** was best for PEST and ToPAS (as well as PASE in active disease)
  - PASE (active disease): 0.09 [1 study; 180 participants; low quality evidence][92]
  - PEST: 0.12 [1 study; 114 participants; very low quality evidence][95]
  - ToPAS: 0.13 [1 study; 257 participants; very low quality evidence][94]
  - PASE: 0.24-0.37 [2 studies; 159 participants; low to very low quality evidence][92,96]
  - PAQ: 0.52-0.68 [2 studies; 279 participants; very low quality evidence][93,95]
  - mPAQ: 0.68-0.71 [1 study; 165 participants; very low quality evidence][93]
- PAQ and mPAQ did not show good diagnostic accuracy for PsA

None of the available screening tools have strong evidence for having very high diagnostic accuracy

7.13.6 Economic Evidence

No relevant economic evidence was identified.

7.14 Recommendations and link to evidence

Recommendations on assessment and referral for psoriatic arthritis	**18. Offer annual assessment for psoriatic arthritis to people with any type of psoriasis. Assessment is especially important within the first 10 years of onset of psoriasis.** **19. Use a validated tool to assess adults for psoriatic arthritis in primary care and specialist settings, for example the Psoriasis Epidemiological Screening Tool (PEST)[l]. Be aware that the PEST does not detect axial arthritis or inflammatory back pain.**
Future research recommendations	**4. What is the validity and accuracy of existing and future screening instruments for PsA in dermatology and primary care settings?** **5. What is the efficacy of the ASAS criteria for identifying inflammatory back pain in a psoriasis population?** **6. What tool can be developed to measure the true burden and cumulative effect of disease activity, severity and impact for a patient suffering from both psoriasis and psoriatic arthritis?**

l See: G. H. Ibrahim, M. H. Buch, C. Lawson, R. Waxman, and P. S. Helliwell. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin.Exp.Rheumatol. 27 (3):469-474, 2009.

Relative values of different outcomes	The GDG agreed that: • Sensitivity is important to capture those people with the disease who need to be referred to a rheumatologist. • Negative predictive value is important to rule out people who do not have PsA. • Practicability is important for a tool to be recommended for use in the primary care setting.
Trade off between clinical benefits and harms	The GDG were aware that regular testing for the presence of PsA could serve as a constant reminder to people with psoriasis that they may develop PsA, which could cause anxiety. The GDG agreed that the benefit of detecting PsA outweighed any potential anxiety caused by testing.
Economic considerations	In the absence of economic evidence about the cost effectiveness of diagnostic tools for PsA, the GDG qualitatively considered the economic implications of recommending a particular tool. The GDG recognised that a highly sensitive tool would result in few false negative diagnoses, thus ensuring that patients with PsA would be quickly and appropriately referred. The review showed that many of the tools had reasonably good sensitivity, but their specificity was less good. False positive diagnoses due to poor specificity risks wasted resources due to inappropriate referral to specialist. However this may be offset to an extent given that people with joint / musculoskeletal symptoms are likely to benefit from specialist rheumatology input, even if these are not due to psoriatic arthritis. The GDG also considered the healthcare setting (e.g.: dermatology clinics, primary care), time taken to complete the assessments and degree of expertise required to use and interpret the scores when considering the potential cost impact of each of the tools. Weighing up all of these issues – sensitivity, specificity and practicability – the GDG considered the PEST questionnaire to offer the best overall balance. The PEST questionnaire is simple, easy to administer and performed well in terms of sensitivity. Its moderate specificity will likely generate referrals which turn out to not to need rheumatologist input, but from their experience the GDG noted that this currently happens in clinical practice. It is likely that formal assessment with the PEST questionnaire, although imperfect, should represent an improvement compared to current practice anyway. Although the clinical evidence indicated that other tools may have slightly better sensitivity (PASE) or specificity (ToPAS), the GDG considered these less practicable to administer.
Quality of evidence	The GDG noted that there were relatively few studies, and the prevalence of PsA varied among the studies. The results of the Gladman study were interpreted with caution as the sample included 52% of people with known PsA. This does not match the specified population and would be likely to increase the apparent sensitivity of the test. The results of the Husni study were interpreted with caution as the

sample excluded difficult to diagnose patients (i.e., when there was disagreement between the rheumatologists regarding the final diagnosis), and this may result in bias.

The results of one study[95] may have been biased owing to the sample including 18.4% of people with known PsA, which does not match the specified population and would be likely to increase the apparent sensitivity of the test. Additionally, not all of the participants were analysed in the calculations but the reasons for drop-out are unclear.

Population selection was agreed to be appropriate if consecutive or random sampling was used, thus avoiding selection bias. The studies investigating ToPAS, PAQ and PEST studies were all appropriate. The studies investigating PASE used unclear population selection methods.

The GDG noted the following issues which applied to the studies in general:

- The threshold for a positive diagnosis was selected after looking at the results and sometimes varied between studies for the same test. This approach would usually be considered to be biased for diagnostic tests. However, the GDG considered this approach to be justified because the studies were initial development and validation studies.
- The order in which the tests were administered (index test and clinical diagnosis) was not always clear and none specified the length of time between the index test and reference standard being performed. However, all participants received the same comparison test regardless of the initial result
- It was not clear if investigators were blinded to the results of the first test when second test was performed.
- None of the tools had been validated in primary care. One study (Ibrahim 2009) assessed PEST and a modified PAQ in a sample from a GP database, but sent the questionnaire by post (so it was not actually completed in a primary care setting).

Although the evidence is either absent or very low quality, the GDG justification making recommendations included:

- PsA is rarely seen so there may be a lack of awareness
- The condition is difficult to diagnose (given the differential diagnoses possible)
- The above two factors may limit diagnostic skills
- PEST is simple, easy to administer and performed well in terms of sensitivity
- Early diagnosis is important because the disease is aggressive and the current treatment strategy is focussed on early treatment, with escalation to biological therapy if need be (see evidence review in chapter 6.3). It is important for patients to be seen by a rheumatologist early if PsA is present. For this reason the GDG made a consensus recommendation in the absence of evidence to assess a person annually for psoriatic arthritis.

Other considerations	• All tools are self-administered. • The GDG noted that the target population for the ToPAS test is people with and without psoriasis, and it includes a section on diagnosing psoriasis. This is irrelevant for the population covered by the guideline who all have known psoriasis. • PEST identifies those who have ever had PsA (i.e., active or inactive) whereas PASE performs differently, depending on whether or not PsA is active. PASE covers disability caused by PsA. • The CASPAR tool was not assessed as it is intended to be used by rheumatologists (validated in rheumatology clinics). • PEST is advantageous in terms of ease of use (only four questions). • PEST score does not cover axial arthritis / inflammatory back pain, however it could be identified from markings on the diagram even though this is not included in the score. The Assessment of Spondyloarthritis International Society (ASAS) criteria[98] can be used to identify inflammatory back pain, but the criteria have not been validated in the psoriasis population. • The GDG chose PEST because it performed better than the other tools for negative predictive value (except PASE in a selected population of only active/easy to diagnose PsA), although it was noted that the tools were not compared in the same population. • The GDG noted that dermatology and primary care healthcare professionals may be seeking different qualities from a test. In primary care, the aim is to detect inflammatory arthritis and generate a referral, the exact type of arthritis is not important. • From GDG experience it was noted that there is a requirement from the dermatology community for a tool that can be used to identify psoriatic arthritis and the GDG had already noted practicability as an important outcome for any tool to be used in primary care. The GDG also noted the variation in skill and exposure to musculoskeletal conditions among non-specialists. Therefore it was felt there is a strong rationale for recommending a tool to detect PsA. • From the expertise of relevant GDG members, it was noted that onset of PsA usually occurs within 10 years of onset of psoriasis, and after 10 years, PsA is less likely to occur. Therefore it may be beneficial from a health economics perspective to recommend more frequent testing in the first 10 years of onset of psoriasis. It was agreed that frequency of tool use would form part of the recommendation. The GDG discussed (and took expert advice about) the frequency of testing and agreed that annual testing within the first ten years of onset of psoriasis is appropriate. • Given that the tools are all self administered the GDG noted the importance of ensuring that healthcare professionals take account of a person's disabilities such as physical, visual or cognitive impairment, linguistic or other communication difficulties and provide help and support. Healthcare professionals will need to ensure that the use of any PsA tool continues to be a sufficiently accurate measure.

7.15 Specialist referral for psoriatic arthritis

It is recognised that psoriatic arthritis may not be a benign disease and can be associated with progressive joint damage, loss of function, increased risk of cardiovascular disease and increased mortality[99]. PsA may cause long-term disability comparable to that seen in rheumatoid arthritis[100]. However, the advent of newer treatment strategies including use of biological agents has demonstrated significant efficacy for people with PsA including improvement in symptoms, physical function, quality of life and reduction of joint damage, at least in the short-term. There is still relatively little known regarding predictors of long-term outcome in people with early disease, or biomarkers that identify those who may have more favourable responses to treatment. Such information would also help inform the need and timing of referral for specialist advice.

PsA may be unrecognised by non-specialists and has associated morbidity. There are implications for the management of psoriasis as well as PsA, as both should be considered together when making decisions about treatment.

In view of this the GDG posed the following question: In people with psoriasis (all types) and suspected psoriatic arthritis, how quickly should referral to a specialist be made in order to minimise the impact of disease on symptoms, joint damage and quality of life?

7.15.1 Methodological introduction

A literature search was conducted for prospective cohort studies or systematic reviews that addressed the question of how quickly referral to a specialist should be made in people with psoriasis and suspected psoriatic arthritis. No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The outcomes considered were:

- Quality of life: HAQ, EQ5D
- Disease symptoms/signs: Pain, tenderness, joint swelling
- Joint damage: Clinical/radiological
- Biochemical markers : CRP and ESR
- Second line therapy (disease-modifying antirheumatic drugs [DMARDs]/anti-TNF-α)
- Mortality
- Cardiovascular events

In the initial search no studies were identified that directly addressed the question. It was therefore decided that indirect evidence from longitudinal studies of patients with early PsA (≤2 years duration of symptoms) would be accepted in order to determine the extent of disease progression over time (in terms of the outcomes listed above). Data on disease severity and rate of progression in patients with early PsA could then inform a discussion by the GDG regarding when to refer. For example, evidence indicating a lack of significant progression in disease severity and functional impairment in recent onset PsA might support delayed referral of such patients and vice versa. Nine prospective observational studies were identified using this search strategy.

However, when the search strategies were re-run in February 2012 to update the review prior to publication one additional prospective cohort study was found that directly addressed the question[101]. Therefore, this study has been considered separately as the most relevant evidence for the GDG to consider in formulating recommendations.

1 A summary of the characteristics of included studies is given in Table 23.

Table 23: Summary of characteristics of included studies

Reference	Study characteristics				Patient characteristics		
	Number of patients	Patient group	Location	Follow-up period	M/F	Mean/median* age at inclusion	Mean/median* duration of arthritis at inclusion
Direct evidence							
Gladman et al., 2011[101]	1077 (436 early PsA; 641 established PsA)	Newly diagnosed and established PsA patients (subgroups analysed)	Toronto	32 years	472/605	Early group: 41.1 years Late group: 45.2 years	Early group: 0.92 years Late group: 11.0 years
Indirect evidence							
Lindqvist et al., 2008 [102]	135	Newly diagnosed PsA patients	Sweden	2 years	57/78	47.3 ±15.2	11.4 ±6.6 months
Cantini et al., 2008 [103]	236	Recent onset PsA patients not responding to 1st line therapy	Italy	Mean 38 months	134/102	45 ±12.4 years	13 ±7.1 months
Bond et al., 2007 [104]	625	Newly diagnosed and established PsA patients	Toronto	Unclear	272/353	*34 years (Range 9-86)	4.5 years (range 0-47.7)
Gladman et al., 2011[101]	1077 (436 early PsA; 641 established PsA)	Newly diagnosed and established PsA patients (subgroups analysed)	Toronto	32 years	472/605	Early group: 41.1 years Late group: 45.2 years	Early group: 0.92 years Late group: 11.0 years
Husted et al., 2005 [105]	341	Newly diagnosed and established PsA patients	Toronto	5.2 years	201/140	45.9 ±12.4 years	10.6 ±8.4 years
Kane et al., 2003 [106]	129	Newly diagnosed PsA patients	Ireland/UK	2 years	68:61	41.2 ±15.1 years	9.9 ±15.1 months
McHugh et al., 2003 [107]	87	Newly diagnosed and established PsA patients (subgroups analysed)	Bath	Median 65 months (range 39-90 months)	38/49	53.5* years (range 2-85)	*11 years (IQR 3.5-17)

Reference	Study characteristics				Patient characteristics		
Queiro-Silva et al., 2003 [108]	71	Newly diagnosed PsA patients	Spain	10 years	44/27	47 ±12 years	<1 year
Punzi et al., 1999 [109]	66	Newly diagnosed PsA patients	Italy	2 years	31/35	Elderly Onset PsA: 65.1 ±6.7 Young Onset PsA: 44.2 ±11.1	<1 year
Harrison et al., 1997 [89]	51	Psoriasis and recent onset inflammatory polyarthritis	Norfolk	1 year	26/25	*52 years	*5.75 months

Due to the nature of the studies considered, GRADE could not be used to assess study quality. Study quality was assessed in a standardised format using the NICE Checklist for Prognostic Studies (NICE Guidelines Manual, 2009[110]). It must also be considered that all of the evidence found in the initial search is indirect for the review question posed as it does not compare the prognosis following early and late referral, which reduces the confidence in its use for decision making. It is also mainly based on non-comparative data or within-group comparisons at different points in follow-up, rather than true cohort studies, making it difficult to assess the differential outcomes of late versus early referral; therefore, most consideration will be given to the study found during the re-run of the search strategy (Table 24). Note that no data were available regarding referral for children with psoriasis and psoriatic arthritis.

Table 24: Study quality checklist

Reference	Quality assessment – methodological flaws of studies						
	Representative population sample	Minimal attrition bias	Prognostic factor measured appropriately	Outcomes adequately measured	Important confounders accounted for	Appropriate statistical analysis	Quality
Direct evidence							
GLADMAN 2011	✓	?	✓	Disease progression			High
				✓	✓[a]	✓	
				Clinic entry characteristics			Moderate
				✓	×	✓	
Indirect evidence							
BOND 2007	✓ Note: not only new onset PsA	✓	✓	✓	✓[b]	✓	Moderate
CANTINI 2008	✓[c]	✓	✓	✓	×	×[d]	Very low
HARRISON 1997	×[e]	✓	✓	×	×	×[d]	Very low
HUSTED 2005	✓	✓	✓	✓	✓[f]	✓	Moderate
KANE 2003	✓	✓[g]	✓	✓	×	×[d]	Very low
LINDQVIST 2008	✓	?	✓	✓	×	×[d]	Very low
MCHUGH 2003	✓	✓	✓	✓	×	✓	Low
PUNZI 1999	✓	?	✓	✓	×	×[d]	Very low
QUEIRO SILVA 2003	✓	?	✓	✓	×	×[d]	Very low

(a) Sex, age, level of education, number of damaged joints at first visit, NSAID use at first visit; DMARD use at first visit; treatment with biologics after first visit; calendar time at clinic entry
(b) Sex, age, arthritis duration, functional class, ESR, tender joint count, swollen joint count and drugs
(c) Note that all required second line drugs
(d) No comparative analysis or time-dependent regression modelling undertaken to compare outcome for different delays in referral
(e) Approximately 50% found to have RA not PsA
(f) Sex, age, duration of PsA, psoriasis severity as measured by the PASI, the number of clinically deformed or damaged joints, and the number of actively inflamed joints updated at each visit
(g) 25% attrition for the 2 year follow-up but the majority of these were still under assessment and had not reached this assessment point

In observational studies it is necessary to control or adjust for confounding variables, other than the prognostic factor being investigated, that may also affect the observed outcomes. Therefore, in assessing study quality the adequacy of controlling for confounders was assessed (see Table 25).

Table 25: Adequacy of controlling for key confounders

Study	Confounder						
	Age	Sex	NSAID/ DMARD use	Arthritis duration	ESR	Calendar time	Joint damage at baseline
GLADMAN2011	✓(a)	✓(a)	✓(a)	✓(b)	×	✓(a)	✓(a)
BOND 2007	✓(a)	✓(a)	✓(a)	✓(a)	✓(a)	×	✓(a)
CANTINI 2008	×	×	×	×	×	×	×
HARRISON 1997	×	×	×	×	×	×	×
HUSTED 2005	✓(a)	✓(a)	×	✓(a)	×	×	✓(a)
KANE 2003	×	×	×	×	×	×	×
LINDQVIST 2008	×	×	×	×	×	×	×
MCHUGH 2003	×	×	×	×	×	×	×
PUNZI 1999	×	×	×	×	×	×	×
QUEIRO SILVA 2003	×	×	×	×	×	×	×

× *Not controlled for*
✓ *Controlled for*
(a) Adjusted for the confounder in statistical analyses
(b) Stratified for this variable

7.15.2 Direct evidence

7.15.2.1 Joint damage and disease symptoms

Evidence profile

The Gladman et al., 2011 study[101] from Toronto followed 1077 patients with new onset (n=436) and established (n=641) PsA and compared the rate of progression of clinical damage in a multivariate analysis. They found that the relative rate of joint damage progression (>2 years vs <2 years disease duration at first visit) was 1.38 (1.08-1.77); p=0.01. This demonstrates a significantly greater rate of clinical damage progression in those referred late in the disease duration compared to early.

A sub-analysis was also performed stratifying the disease duration at first visit into six groups (see Table 26).

Table 26: Relative joint damage rate stratified by disease duration at clinic entry

Duration of disease at first visit	N	Relative rate of joint damage progression (95% CI)	P value
1-2 years vs <1 year	212	1.53 (0.99-2.36)	0.05
2-4 years vs <1 year	248	1.70 (1.11-2.62)	0.01
5-9 years vs <1 year	201	1.83 (1.16-2.88)	0.009
10-20 years vs <1 year	204	1.83 (1.14-2.96)	0.01
>20 years vs <1 year	86	2.96 (1.64-5.34)	0.0003

They also showed that at first visit those who had been referred early in the disease course had significantly less radiographic damage (39.2% vs 65.9%; p<0.0001) and fewer damaged joints (mean 3.5 vs 9.2; p<0.0001) at clinic entry, although the mean number of actively inflamed joints was similar (10.5 vs 11.7; p=0.239).

Evidence statements

In people with psoriasis and PsA:

- There is a statistically significantly greater risk of clinical joint damage progression in those referred late (>2 years after onset) compared with those referred early (<2 years after onset) [1 study; 1077 participants; high quality evidence][101]
- The earlier referral is made to a rheumatology clinic the less joint damage progression is seen in subsequent years [1 study; 1077 participants; high quality evidence][101]
- Those with early disease (<2 years after onset) have significantly less radiographic damage and fewer damage joints at clinic entry compared with those with late disease (>2 years after onset) [1 study; 1077 participants; moderate quality evidence][101]
- There was no statistically significant different in mean number of actively inflamed joints at clinic entry between those with early and late disease [1 study; 1077 participants; moderate quality evidence][101]

7.15.3 Indirect evidence

7.15.3.1 Joint damage

Evidence profile

The Bond et al., 2007 study [104] from Toronto followed 625 patients with new onset and established PsA. Single and multi-factor analyses were performed on the data and a statistically significant relationship was identified between disease duration prior to clinic entry and clinically damaged joint count. Arthritis duration at first visit was found to be a predictor for progression in clinically measured damage in patients without damage at first visit, with the change in the number of permanently damaged joints or relative damage rate being 1.54 (1.22-1.96) per decade (p<0.001); but not in those with existing damage (RDR: 1.06 (0.92-1.22) per decade (p=0.39). So, in summary, the longer the duration of arthritis before entry to the clinic, the more joint damage caused if there was no damage initially, but once a patient has a damaged joint, the importance of arthritis duration for prognosis diminishes.

However, based on radiological assessment of damage, there was no statistically significant effect of PsA duration prior to clinic entry on relative damage rate regardless of whether joint damage was present at baseline or not (RDR 0.99 (0.81-1.19) per decade (p=0.88) if damage was present and 0.84 (0.63-1.12) per decade (p=0.23) if no damage was present at first visit).

Conversely, the relative damage rate (95% CI) was 0.67 (0.55 to 0.8) per extra decade in clinic (single factor analysis) p<0.001, and 0.73 (0.6 to 0.89) per extra decade in clinic (all factors included) p<0.001. This suggests that in the clinic the opposite effect occurs, with longer follow-up decreasing the damage, suggesting that the initiation of care was effective.

Queiro-Silva et al., 2003 [108] reported no statistically significant difference in average duration of arthritis in patients with erosive and non-erosive PsA (mean ±SD: 8 ±7 months versus 10±6 months).

McHugh et al., 2003 [107] followed-up 87 patients with newly diagnosed and established PsA. Thirteen of these patients had disease duration of less than 1 year at time of entry into the study (i.e. recent onset). The rate of peripheral joint progression was significantly higher in this group (compared to baseline assessment) versus the rate of joint damage progression in the same patients over subsequent years until follow-up (4.0 vs. 0.32, P=0.003). This suggests that the highest rate of peripheral joint involvement may be within 12 months of disease onset, but steady progression of peripheral joint involvement occurs among those referred to a clinic (0.43 joints per year for full sample and 0.32 joint per year for those referred within one year of diagnosis).

Table 27: Radiological damage over time reported in studies of early PsA

Time point	Linqvist, 2008	Kane, 2003	Queiro-Silva, 2003	Harrison, 1997
Erosions at 0 yr	24/120 (20%)	32/117 (27%)		-
Erosions at 1yr	-	-		7/32 (22%)
Erosions at 2yr	23/79 (32%)	40/86 (47%)		-
Erosions at <2yr			32/71 (45%)	

Further evidence of radiological damage in early PsA comes from five studies with average follow-up times ranging from 0 to 10 years (Table 27)

- In the Lindqvist, 2008 [102] study, radiological examination was performed in 120 patients with early onset confirmed PsA on inclusion. 24 patients (18%) had radiological changes compatible with PsA at inclusion, increasing (NS) to 33 patients (24%) at 2 years follow-up.
- In the Kane, 2003 [106] study, radiographs were performed at baseline in 117 patients. 32 (27%) patients had erosions, 24 (19%) patients had joint space narrowing and 22 (19%) patients had periostitis. After a median 24 months follow-up, 86 patients had radiographs and 40 (47%) patients had erosions, 32 (37%) had joint space narrowing and 25 (29%) patients had periostitis. These changes occurred despite early DMARD use; however, there is a risk of bias in the selection of patients who received radiographs.
- Queiro-Silva et al., 2003 [108] followed 71 early PsA patients, who did not have radiographical evidence of erosions at presentation, for an average period of 10 years. Mean ±SD time to detect erosions or narrowing of joint spaces was 20 ±4 months and, by the end of follow-up, 32/71 (45%) had developed erosive and deforming arthritis.
- Harrison et al., 1997 [89] reported radiographic evidence of erosions at 1 year as 22%, however baseline levels were not reported.
- The Punzi, 1999 [109] study compared Elderly Onset early PsA (EOPsA) and Younger Onset early PsA patients (YOPsA), presenting the mean number of erosions per person rather than the number with erosions. At presentation the mean number of erosions was 2.3 ±2.1 (EOPsA), 2.2 ±2.2 (YOPsA) in hands, and 2.7 ±1.2 (EOPsA), 1.1 ±1.1 (YOPsA) in feet. After two years follow-up there were a mean number of erosions of 4.4±3.0 (EOPsA), 2.7±2.0 (YOPsA) in hands, and 4.7±2.2 (EOPsA), 2.1±1.2 (YOPsA) in feet. There was a trend towards an increase in hand and foot erosions in EOPsA patients and a trend towards an increase in foot erosions alone in the YOPsA group.

- The Punzi, 1999 [109] study also showed a higher number of active joints in elderly vs young onset PsA at both baseline (12.2±6.3 vs 6.7±6.6; p<0.001) and 2-year follow-up (8.1±4.2 vs 4.7±3.6; NS)

Evidence statements

In people with psoriasis and recent onset (≤2 years) PsA:

- 18-27% had radiological erosions around the time of clinic entry and up to half of patients developed radiographic evidence of joint destruction after an average of 0 to 10 years follow-up (one study reported a mean time to detect erosions/joint space narrowing of 20 months from baseline) [4 studies; 386 participants; very low quality evidence] [89,102,106,108,109]
- Early stages of PsA are associated with a more volatile disease state, and there is some evidence to suggest that the longer the time period before referral to a specialist clinic the greater the risk of clinical joint damage over time (assuming damage not already present at referral). [2 studies, 712 participants; low to moderate quality evidence] [104,107]. However, the same predictive value of PsA duration was not seen for the outcome of radiographic joint damage [1 study, 625 participants; moderate quality evidence][104]
- PsA may have a more aggressive onset and severe prognosis among the elderly [1 study, 66 participants; very low quality evidence] [109]

7.15.3.2 Remission

Evidence profile

A range of remission rates has been reported among people referred with early PsA. Relatively low remission rates, despite treatment in specialist rheumatology clinics, were reported in one study[89], which reported 6% of patients in remission at 1 year.

However, higher remission rates were reported in three studies. Kane et al., 2003[106] reported remission rates of 26% and 21% at 1 and 2 years respectively (with conventional therapy) and spontaneous (DMARD-free) remission in 11-12% of patients. Lindqvist et al., 2008[102] reported 17% of patients as in remission after 2 years of follow-up. In the Cantini et al., 2008[103] study of 236 patients with early PsA requiring second-line therapy, 32.6% were in remission after an average follow-up time of 38 months.

Evidence statements

In people with psoriasis and recent onset (≤2 years) PsA:

- The proportion in remission (with or without conventional therapy) after between 1 year and 36 months of follow-up ranged from 4.6% to 26% [4 studies; 551 participants; very low quality evidence] [89,102,103,106]

7.15.3.3 Quality of life

Evidence profile

Quality of life was reported in terms of the Health Assessment Questionnaire (HAQ) score, where scores of 0-1 represent mild to moderate difficulty, 1-2 moderate to severe disability, and 2-3 severe to very severe disability.

Three studies of recent onset PsA reported an improvement in HAQ over time. Harrison et al., 1997[89] reported a reduction in median HAQ score from 0.63 at baseline to 0.44 at 1 year follow-up. Lindqvist

et al., 2008[102] reported a non-significant reduction in mean HAQ score in recent onset PsA patients from 0.66 ±0.56 at inclusion to 0.55 ±0.79 at 2 year follow-up. The Kane et al., 2003[106] study reported a reduction in mean HAQ score from 0.71 ±0.64 at baseline to 0.4 ±0.6 at years 1 and 2 of follow-up, also suggesting a trend towards improvement.

Husted et al., 2005[105] reported outcomes from the Toronto data based on functional impairment after a mean follow-up period of 5.2 years. A Markov model was used to model transitions from various states of disability (state 1 = mild, state 2 = moderate, state 3 = severe) mapped to HAQ scores. In a multivariate model of predictors of transitions between these disability states, there was a significantly lower rate of transition state worsening in patients with PsA duration >5 years compared to those with duration <2 years (RR 0.33 [95% CI 0.14 to 0.76]). There was also a significantly lower rate of transition state improvement in patients with PsA duration >5 years compared to those with duration <2 years (0.44 [95% CI 0.21 to 0.90]). Overall, patients with duration of PsA 2-5 years and >5 years had a reduction in transition rates of 56-70% compared with those patients with PsA duration <2 years, suggesting a more stable disease course over time (with treatment).

Evidence statements

In people with psoriasis and recent onset (≤2 years) PsA:

- A trend in quality of life improvement, as measured by HAQ score, is reported over time [2 studies, 315 participants; very low quality evidence] [89,102,106].
- Functional impairment is more variable in the early stages of PsA (first 2 years) compared to established disease [1 study, 341 participants; moderate quality evidence] [105]

7.15.3.4 Second line therapy (disease-modifying anti-rheumatic drugs [DMARDs]/anti-TNF-α)

Evidence profile

Six studies reported DMARD use in patients with early PsA. In the Punzi et al., 1999[109] study no patients were on DMARDs at inclusion, however after 2 years, 84% of Younger Onset PsA patients and 94% of Elderly Onset PsA patients were on DMARDs. Furthermore, in the Harrison et al., 1997[89] study 41% of patients were on DMARD therapy after 1 year of follow-up. In the Kane et al., 2003 study[106] 12% were on DMARDs at inclusion and this increased to 59% at 1 year and 56% at 2 years. Linqvist et al., 2008[102] reported that 38% of patients were on DMARD therapy on inclusion (within 2 years of onset of symptoms), although DMARD use at follow-up was not reported. Queiro-Silva et al., 2003[108] reported DMARD use in 68% of early PsA patients after 10 years of follow-up.

In the Cantini et al., 2008[103] study both DMARD and biological use was reported. After a mean follow-up time of 38 months, 68% were on DMARD therapy and 32% were on anti-TNF-α biological therapy (plus methotrexate). Note that all were receiving second-line therapy at inclusion

Evidence statements

In people with psoriasis and early onset (≤2 years symptom duration) PsA:

- 41% to 94% of patients required DMARDs after an average of 1 to 10 years follow-up [6 studies, 688 participants; very low quality evidence] [89,102,103,106,108,109]
- 32% of patients required anti-TNF-α biological therapy after an average 38 months follow-up [1 study, 236 participants; very low quality evidence] [103]

7.15.3.5 Disease symptoms/signs (pain/swelling/deformity)

Evidence profile

The Lindqvist et al., 2008[102] study reported a statistically significant (p≤0.05) improvement in the number of swollen joints (4.4 ±4.5 to 1.8 ±3.4) and tender joints (5.8 ±6.7 to 3.6 ±6.7) from entry to 2 years follow-up. Similarly, there was a statistically significant (p≤0.05) improvement in pain, as measured by the visual analogue score (VAS; 0-100 mm), from 44 ±24 to 34 ±26 mm. Kane et al., 2003[106] also reported reductions in pain scores, with VAS decreasing from 4.8 ±2.7 mm at baseline to 3.1 ±3 mm at 1 year and 3.4 ±2.7 mm at 2 years follow-up. Mean swollen joint count also decreased, with a reduction from 6.9 ±8 at baseline to 2.9 ±5.2 at 1 year and 2.4 ±4.1 at 2 years follow-up. Harrison et al., 1997[89] reported a reduction in median number of swollen joints from 7 (range 0-32) at baseline to 4 (range 0-16) at 1 year.

Evidence statements

In people with psoriasis and early onset (≤2 years symptom duration) PsA:

- There was a statistically significant improvement from baseline in pain scores (VAS) after 2 years of follow-up [2 studies, 264 participants; very low quality evidence][102,106]
- There was statistically significant improvement in the number of swollen joints and tender joints after 2 years of follow-up [3 studies, 315 participants; very low quality evidence] [89,102,106]

7.15.3.6 Biochemical markers (erythrocyte sedimentation rate/C-reactive Protein)

Evidence profile

The Lindqvist et al., 2008[102] study reported a statistically significant (P <0.05) mean decrease in Erythrocyte Sedimentation Rate (ESR) (from 17.3 ±17.9 to 11.2 ±10.2 mm/h) and C-reactive protein (CRP) (from 14.7 ±21.9 mg/l to 7.2 ±7.6 mg/l) between entry and 2 year follow-up. In a study of new onset PsA, Kane et al., 2003[106] reported a mean reduction in ESR from 24 ±27 mm/h at baseline to 13 ±15 mm/h at 1 year and 12 ±14 mm/h at 2 years follow-up. Similarly, mean CRP levels decreased from 28 ±59 mg/l at baseline to 10 ±14 mg/l at 1 year and 8 ±12 mg/l at 2 year follow-up.

Punzi et al.,1999[109] reported a decrease in mean ESR from 64.2 ±65.3 mm/h at baseline to 38.4 ±15.2 mm/h after 2 years' follow-up in Elderly Onset PsA patients and a more modest decrease from 30.5 ±30.0 mm/h to 26.3 ±15.0 mm/h in Younger Onset PsA patients. Mean CRP levels also decreased in both groups: 3.9 ±2.0 mg/l to 2.2 ±1.0 mg/l in Elderly Onset PsA and 1.33 ±1.3 mg/l to 0.9 ±0.9 mg/l in Younger Onset PsA patients.

Evidence statements

In people with psoriasis and early PsA:

- There is a statistically significant reduction from baseline values in ESR and CRP following referral to a rheumatology clinic [3 studies, 330 participants; very low quality evidence] [102,106,109]

7.15.4 Economic evidence

No relevant economic evidence was identified.

7.16 Recommendations and link to evidence

Recommendations on	**20.As soon as psoriatic arthritis is suspected, refer the person to a**

assessment and referral for psoriatic arthritis	**rheumatologist for assessment and advice about planning their care.**
Future research recommendations	**7. What is the natural history of psoriatic arthritis and are there any adverse prognostic markers that identify individuals at risk of severe/aggressive/destructive disease?**
Relative values of different outcomes	The GDG prioritised the following outcomes: • Quality of life • Symptoms and signs • Joint damage • Mortality • Cardiovascular events
Trade off between clinical benefits and harms	Psoriatic arthritis can be a volatile, destructive condition for which there are interventions of proven benefit. In addition, future management of skin psoriasis may be affected by a diagnosis of psoriatic arthritis and allow use of interventions that would benefit both conditions. The GDG agreed that the benefits of an accurate PsA diagnosis and specialist management outweigh any potential harm of early specialist referral (patient anxiety, unnecessary hospital attendances, impact on rheumatology services, cost). The use of the recommended screen tool (PEST) should avoid to some degree other causes of musculoskeletal symptoms which can be dealt with by non-specialists (in primary care).
Economic considerations	In the absence of economic evidence about timing of referral for people with suspected psoriatic arthritis, the GDG qualitatively considered the health economic implications of recommending early referral. They focused primarily on the substantial health burden of PsA, as a chronic, lifelong disorder. It is a lifelong disorder and its impact on patients' functional status and quality of life fluctuates over time. The combination of skin and joint disease results in significant impairment of quality of life and psychosocial disability, with patients scoring significantly worse on health-related quality of life domains such as physical mobility, pain, energy, sleep, social isolation and emotional reaction. The evidence shows that PsA is an aggressive disease with particular volatility during the early stages, thus supporting an early and aggressive treatment strategy. The GDG concluded that due to the significant effect of PsA on a patient's HRQoL, PsA should be diagnosed early and treated aggressively in order to minimise joint damage and skin disease.
Quality of evidence	No randomised controlled trials were found (as expected). The evidence considered by the GDG is from observational studies. It was not possible to apply GRADE to assess the quality of the studies, as the studies did not involve a comparison. The NICE checklist for prognostic studies was used to assess quality. All of the evidence found in the initial search was indirect for the review question posed, which reduces the confidence in its use for decision making. It was also mainly based on non-comparative data or within-

	group comparisons at different points in follow-up, rather than true cohort studies, making it difficult to assess the differential outcomes of late versus early referral. However, a study[101] directly addressing the review question was identified during re-runs that was graded as moderate to high quality evidence. The GDG gave most weight to the data reported in this study when formulating recommendations. From the indirect evidence there were three studies[104,105,107] that performed appropriate statistical analyses, and two of these adjusted for confounders[104,105]. All other studies had limitations and hence were graded as very low quality evidence. HAQ score during the early stage of PsA is influenced by joint inflammation and is reversible. With longer disease duration, HAQ score becomes a marker of disease severity and joint inflammation, and is less likely to improve. Therefore HAQ score is influenced by disease duration of the study cohort.
Other considerations	The evidence shows that PsA is an aggressive disease and is volatile in the early stages, particularly within the first two years. Many of the studies were carried out before biological agents were introduced and therefore do not reflect current clinical practice. It is now known that DMARDS are not the most effective treatment option for PsA. It was recognised that with the advent of biologics there is now a definite move towards a treat to target strategy that should allow more effective treatments for patients in need of them, which makes it more important for early PsA to be seen and assessed for risk factors for progression as early treatment will be more effective than was seen in the studies. Joint damage and impact on quality of life occur early in the disease, so there is no good reason to delay referral to a rheumatologist. Radiological damage to joints is more likely to occur in joints that have been persistently inflamed. In clinical practice it is difficult to predict which people with PsA will need second line treatment. From GDG experience, multiple swollen joints, high C -reactive protein (CRP) levels or erythrocyte sedimentation rate (ESR) and evidence of structural damage to joints are adverse prognostic factors. The GDG were aware of the technology appraisals for the use of biological agents to treat PsA.[111,112] The GDG agreed that all people with psoriasis should be evaluated for PsA (see section 6.2) and that people in whom PsA is suspected should be referred to a rheumatologist. The referral should be rapid due to the volatile and progressive nature of the disease. There is evidence that referral should be made within the first year, as one in five people will develop preventable joint erosions.

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7.17 Identification of comorbidities

Psoriasis has been traditionally considered primarily an inflammatory disease affecting the skin, with associated arthritis occurring in a proportion of patients. However, a number of recent studies suggest that people with psoriasis also have an increased morbidity and mortality due to cardiovascular disease. It has been postulated that this risk, analogous to observations in rheumatoid arthritis, is due to the effects of inflammation (i.e. psoriasis per se), although the prevalence of traditional risk factors for cardiovascular disease such has hypertension, obesity, smoking, excess alcohol intake and hyperlipidaemia are also reported to be higher in people with psoriasis and are likely to contribute to CVD risk. Clustering of truncal obesity, insulin resistance, hypertension and dyslipidaemia (known as the metabolic syndrome) is also reported to be more prevalent in psoriasis and carries with it elevated risk of multiple problems including cardiovascular and liver disease (obesity-related or non alcoholic fatty liver disease). Setting aside skin cancer (see section 6.7), certain cancers have variously been reported as more common in people with psoriasis including lymphoma.

Such observations, if shown to be scientifically robust, have important implications for people with psoriasis and health care professionals involved in the delivery of care. Firstly, co-morbid conditions add to the complexity of treatment and may adversely impact on the side effect profile or efficacy of therapies used to treat psoriasis. Equally, some of the treatments used in psoriasis may adversely impact on associated co-morbidities such as ciclosporin which, as example, can lead to both hypertension and hyperlipidaemia. Secondly, if people with psoriasis are at significantly increased risk of certain co-morbidities, there is the opportunity to devise pathways of care that encompass all aspects of patients' health that would be beneficial in terms of improved awareness, earlier treatment of modifiable risk factors, convenience and time, and also, health care resource. In this question, we are therefore interested to establish whether people with psoriasis are at risk of particular co-morbidities, and the size of this risk.

A second aspect to this question is whether there are particular groups of people with psoriasis that are at increased risk, over and above those ones that are already well established such as smoking or obesity. National guidelines already exist[113-115] for addressing many suspected co-morbid conditions since they are common in the general population anyway. However, if evidence exists that the prevalence is significantly greater in particular subgroups of people with psoriasis, such as those with more severe psoriasis, focussed delivery of care becomes even more cost effective and realistic. As importantly, if there are groups of people with psoriasis who are not at increased risk of, for example, cardiovascular disease, these individuals can be reassured, and do not need to be screened or labelled as 'at risk' of what may be potentially stigmatising and/or worrying conditions.

The GDG agreed to ask the following question: Are people with psoriasis (all types) at higher risk than people without psoriasis for significant comorbidities and are there subgroups within the psoriasis population at a further increased risk?

7.17.1 Clinical methodological introduction

7.17.1.1 Review protocol

A literature search was conducted for systematic reviews, RCTs or cohort studies that addressed whether the incidence of specific comorbidities is increased in people with psoriasis and whether there are subgroups of the population with psoriasis who are at particularly high risk.

No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded and the analyses had to be compared with a matched control group or adjusted for confounders.

The prognostic factor was psoriasis (mild or severe) compared with a reference cohort of people without psoriasis (the unexposed cohort) unless otherwise stated.

The outcomes considered were:

- Incidence of comorbidities:
  - Obesity
  - Cardiovascular disease (including stroke)
  - Alcohol-related disease
  - Cancer (stratified as: skin cancer, lymphoma, or all cancer)
  - Liver disease
  - Diabetes mellitus
  - Hypertension
  - Depression
  - Inflammatory bowel disease
- Death

Subgroup analyses were performed, where possible, for the following prognostic factors:

- Disease severity (may be indicated by hospital admission or treatment in secondary care)
- Particular treatments used (e.g., phototherapy or immunosuppressive drug use)
- Lifestyle markers (smoking and alcohol use)
- Age

7.17.2.2 Included studies

Thirty three studies [3,5,6,116-145] were found that addressed the question and were included in the review. None of these studies addressed the incidence of comorbidities in children with psoriasis.

Note that the studies were population-based cohorts and in large observational studies of this type there is the risk of misclassification. A majority were retrospective studies which can have a higher risk of bias related to the recording of baseline data, the need for imputation and potential selection bias. However, the data were sourced from large databases, and many used the GPRD which is prospectively collected by GPs and includes comprehensive patient data.

A summary of the characteristics of included studies is provided in Table 28.

Table 28: Summary of characteristics of included studies

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
ABUABARA 2010	17933 (3603 with psoriasis)	GPRD – severe psoriasis (psoriasis diagnostic code and history of systemic therapy)	GPRD – no psoriasis diagnostic codes (matched by practice, index date and date of registration)	UK	3.40 ± 2.76 in control and 3.43 ± 2.73 in severe psoriasis group	• Risk of death	• Inpatients included so more likely to have severe psoriasis.
ABUABARA 2011	25,554 with psoriasis: phototherapy group n=4220; systemics group n=20094	Claims database (covering 50% US hospitals) – psoriasis treated with systemic therapy	Claims database (covering 50% US hospitals) – psoriasis treated with phototherapy	USA	Unclear (mean duration of treatment: 243-591 days)	• Acute myocardial infarction	• Comparing two psoriasis cohorts • Unclear reporting • Few participants in each subgroup
AHLEHOFF 2011	4164739 (38,664 with psoriasis (35,138 mild and 3526 severe))	Danish National Patient Register – claims for vitamin D analogues (the severe subgroup were defined by hospitalisations (including out-patient visits) for psoriasis or psoriatic arthritis)	Danish National Patient Register – entire Danish population	Denmark	Maximum 10 years	• Incidence of venous thromboembolism	• Only included new-onset psoriasis • Excluded those with a history of venous thromboembolism • Psoriasis identified by claims for vitamin D analogues • Stratified by mild and severe psoriasis and by age • Definition of severity included hospitalisation for PsA (so this could be a misclassification if only the joints are severely affected) • Unable to identify patients treated with topical corticosteroids alone

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
							(selection bias) and also unable to address the potential impact of various systemic treatment strategies
AHLEHOFF 2011B	49397 (462 with psoriasis)	Danish National Patient Register – claims for vitamin D analogues plus first MI 2002-2006	Danish National Patient Register – all with first MI 2002-2006 from the entire Danish population	Denmark	Maximum 10 years (also reports 30 day and 1 year prognosis)	• Incidence of all-cause mortality • Incidence of a composite of recurrent myocardial infarction, stroke and cardiovascular death	• Limited to those already known to have experienced first-time myocardial infarction during 2002-2006, and compares risk of death and further cardiovascular events in those with and without psoriasis • Psoriasis identified by claims for vitamin D analogues • Unable to identify patients treated with topical corticosteroids alone (selection bias) and also unable to address the potential impact of various systemic treatment strategies
AHLEHOFF 2011D	4040257 (36,992 with psoriasis (34,371 mild and 2621 severe))	Danish National Patient Register – claims for vitamin D analogues (the severe subgroup were defined by hospitalisations (including out-patient visits) for psoriasis or psoriatic arthritis)	Danish National Patient Register – entire Danish population	Denmark	Maximum 10 years	• Incidence of all-cause mortality • Incidence of cardiovascular mortality • Incidence of hospitalisation for myocardial infarction, stroke and coronary revascularisation	• Only included new-onset psoriasis • Excluded those with diabetes or atherosclerotic disease • Psoriasis identified by claims for vitamin D analogues • Stratified by mild and severe psoriasis and by age • Definition of severity included hospitalisation for PsA (so this could be a misclassification if only the joints are severely affected)

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
							• Unable to identify patients treated with topical corticosteroids alone (selection bias) and also unable to address the potential impact of various systemic treatment strategies
AHLEHOFF 2011E	4518484 (39,558 with psoriasis (36,765 mild and 2793 severe))	Danish National Patient Register – claims for vitamin D analogues (the severe subgroup were defined by hospitalisations (including out-patient visits) for psoriasis or psoriatic arthritis)	Danish National Patient Register – entire Danish population	Denmark	Maximum 10 years	• Incidence of first-time ischaemic stroke	• Only included new-onset psoriasis • Excluded those with prevalent ischaemic stroke • Psoriasis identified by claims for vitamin D analogues • Stratified by mild and severe psoriasis and by age • Definition of severity included hospitalisation for PsA (so this could be a misclassification if only the joints are severely affected) • Unable to identify patients treated with topical corticosteroids alone (selection bias) and also unable to address the potential impact of various systemic treatment strategies
BOFFETTA 2001	9773 with psoriasis	Swedish National Board of Health and Welfare In-patient Register – hospital discharge diagnosis of	General Swedish population	Sweden	15+ years, no mean given	• Incidence of cancer • Risk of mortality	• Excluded the first year of observation following the index admission • Lack of data on treatment • People hospitalised for psoriasis

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
		psoriasis (ICD code)					
BRAUCHLI 2008	65449 (32593 with psoriasis)	GPRD – first-time psoriasis diagnosis 1994-2005	GPRD – no psoriasis diagnosis; matched on age, sex, practice and years of history in GPRD	UK	Followed until diagnosis of diabetes, death or no further medical record.	• Incidence of diabetes	• Excluded those with a diagnosis of diabetes or use of anti-diabetic drugs 30 days prior to first diagnosis of diabetes. • There was a nested case-control within the cohort study which was excluded based on study design. • Used a defined algorithm to reduce the likelihood of misclassification. • Did not have many patients with the highest disease severity. • Adjusted for BMI.
BRAUCHLI 2009	73404 (33,760 with psoriasis)	GPRD – first-time psoriasis diagnosis 1994-2005	GPRD – no psoriasis diagnosis; matched on age, sex, practice and years of history in GPRD	UK	Mean 4.6 years; maximum 11 years	• Incidence of cancer	• There was a nested case-control within the cohort study which we excluded based on study design. • Excluded those with history of cancer or HIV and those with <3 years of history in the database before first-time psoriasis diagnosis (or the corresponding date in the control group) • The number exposed to oral therapies was low and so information on this subgroup, which may have the greatest severity, is limited

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
BRAUCHLI 2009A	73,404 (36,702 with psoriasis)	GPRD – first-time psoriasis diagnosis 1994-2005	GPRD – matched on age, sex, practice and years of history in GPRD	UK	Mean 4.6 years	• Incidence of myocardial infarction • Incidence of stroke • Incidence of transient ischaemic attack	• There was a nested case-control within the cohort study which we excluded based on study design • Excluded patients with a history of isolated systolic hypertension or cerebrovascular diseases, cancer or HIV prior to the psoriasis diagnosis and those with <3 years of history in the database prior to the first-time psoriasis diagnosis (or the corresponding date in the control group) • Short follow-up as chronic systemic inflammation may take longer to cause adverse cardiovascular outcomes • Inception cohort study – only included those with a first-time diagnosis of psoriasis and subsequent CVD
CHEN 2011	203,686 (3686 with psoriasis)	Longitudinal Health Insurance Database – first-time diagnosis of psoriasis according to ICD codes	Longitudinal Health Insurance Database – no psoriasis diagnostic codes	Taiwan	Min 1.5 and max 10 years	• Incidence of cancer	• Excluded those with unclear baseline data e.g., conflicting gender or uncertain birth date; history of cancer before diagnosis of psoriasis or before first-time inclusion in this cohort • Stratified data for age and prior treatments
FRENTZ 1999	6905 with psoriasis	Danish Hospital Discharge	General Danish population	Denmark	9.3 years (range 0-17	• Incidence of cancer	• The register-based design does not give access to information on

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
		diagnosis of psoriasis			years)		individual treatment schedules through time.
GELFAND 2003	107921 (1718 with psoriasis)	GPRD – psoriasis diagnosis plus 65 years or older	GPRD – no psoriasis diagnostic codes	UK	Median time in months (25th, 75th percentile): 39.75 (19.1, 65.1) psoriasis group; 46 (20.8, 73.1) non-psoriasis group	• Incidence of lymphoma • Incidence of internal malignancy	• Excluded those with a history of one of the outcome diseases prior to study entry or developed within 6 months of study entry. • Population was a sample of 10% of the patients who were 65 years or older since the incidence of cancer increases with age.
GELFAND 2006	919147 (153,197 with psoriasis (149,203 mild and 3994 severe))	GPRD – psoriasis diagnosis (severe subgroup defined by history of systemic therapy for psoriasis)	GPRD – no psoriasis diagnostic codes (matched by practice and index date)	UK	Mean ~5 years	• Incidence of lymphoma • Incidence of non-Hodgkin lymphoma • Incidence of Hodgkin lymphoma • Incidence of T-cell lymphoma	• Psoriasis patients were older than the control patients and the mild psoriasis patients were slightly more likely to be females • Misclassification of certain psoriasis therapies • Severe group relatively small • Did not exclude those with a history of lymphoma
GELFAND 2006A	697971 (130976 psoriasis patients (127139 mild and 3837 severe))	GPRD – psoriasis diagnosis (severe subgroup defined by history of systemic therapy for psoriasis)	GPRD – no psoriasis diagnostic codes (matched by practice)	UK	Mean follow-up 5.4 years	• Incidence of myocardial infarction	• Severe psoriasis was defined as those who had received systemic therapy; therefore, any difference may be due to disease severity or to systemic therapy. However, the most commonly used drug was methotrexate, which has been shown in other studies to lower the incidence of cardiovascular outcomes, so the risk of myocardial infarction may be an underestimate

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
							• Included patients with a history of myocardial infarction • MI had to be subsequent to psoriasis diagnosis
GELFAND 2007	712,952 (133,568 mild psoriasis; 2951 severe psoriasis)	GPRD – psoriasis diagnosis (severe subgroup defined by history of systemic therapy for psoriasis)	GPRD – no psoriasis diagnostic codes (matched by practice, and date of registration)	UK	Mean 4-5 years	• Incidence of death	• Did not examine only new-onset psoriasis because this was difficult to identify from the database, so if they had died before entering cohort they may have underestimated the risk of death. • Severe psoriasis patients were included from the first time documented rather than first time classified • The severe group was relatively small
GELFAND 2009	643742 (129,143 with mild psoriasis; 3603 with severe psoriasis)	GPRD – psoriasis diagnosis (severe subgroup defined by history of systemic therapy for psoriasis)	GPRD – no psoriasis diagnostic codes (matched by practice, index date and date of registration)	UK	3-4 years mean and 2-3 years standard deviation	• Incidence of stroke • Risk of stroke for mild and severe psoriasis patients	• Did not include BMI as a covariate in the primary analysis as only recorded for 65% of patients
HANNUKSELA- SVHAN 2000	5687 with psoriasis	Finnish Hospital Discharge registry – psoriasis diagnosis	Entire Finnish population	Finland	Mean 14 years	• Incidence of cancer	• Cancer registry is virtually complete in Finland and so technical deficiencies are unlikely to bias results. • Not possible to record the number of skin checks for cancer in

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
							relation to severity of psoriasis and to the number of treatments • Patients hospitalised for psoriasis
JI 2009	15858 with psoriasis	Swedish Hospital Discharge registry – hospitalised for psoriasis	Swedish hospital Discharge registry – no psoriasis	Sweden	Median 10 years (range 0-40 years)	• Incidence of cancer	• Possible confounding factors such as alcohol and smoking not accounted for • Not directly applicable to all psoriasis patients as hospitalised patients must represent a severe subgroup
KAYE 2008	263948 (44,164 with psoriasis)	GPRD – first-time psoriasis diagnosis after 1st January 1991	GPRD – matched for age, sex, practice and index date	UK	1,3, 5 and 10 year follow-up	• Incidence of myocardial infarction • Incidence of diabetes • Incidence of hypertension • Incidence of obesity • Incidence of hyperlipidaemia • Incidence of angina • Incidence of atherosclerosis • Incidence of peripheral vascular diseases • Incidence of stroke	• Did not adjust for confounders for cardiovascular disease such as smoking • No validation of stroke cases • Only included those with CVD diagnoses after first diagnosis of psoriasis and excluded those with outcome of interest before index date • At least 1 year medical history in database before index date
KURD 2010	916948	GPRD –psoriasis	GPRD – no	UK	Not reported	• Incidence of	• Risk of misclassification of severe

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
	(146042 with mild psoriasis; 3956 with severe psoriasis)	diagnostic code (severe subgroup defined by history of systemic therapy for psoriasis)	psoriasis diagnostic code (matched on index date)		but followed up until reached outcome of interest, transferred out, death or practice no longer 'up to standard'	depression	psoriasis because defined by use of systemic psoriasis treatment. Some patients with severe psoriasis may not receive systemic treatment and will have been misclassified as having mild disease.
LI 2011	184395 (3074 with psoriasis)	Nurses Health Study and Health Professionals Follow-up Study – self-report of psoriasis diagnosis	Nurses Health Study and Health Professionals Follow-up Study – no psoriasis diagnosis reported	USA	Unclear	• Incidence of Type 2 diabetes	• Psoriasis and diabetes assessed by self-report • Mainly female and all health care practitioners
LIN 2011	28512 (4752 psoriasis)	Taiwan National Health Research Institute (NHRI) database – visited ambulatory care centres for psoriasis	NHRI database – matched by age and sex	Taiwan	5 years	• Incidence of acute myocardial infarction	• Excluded patients with a diagnosis of acute myocardial infarction. • Myocardial infarction had to be subsequent to psoriasis diagnosis
MALLBRIS 2004	28748 with psoriasis	Swedish in-patient registry – discharge diagnosis of psoriasis	Swedish general population	Sweden	15 years or more	• Incidence of mortality from isolated systolic hypertension • Incidence of mortality from cerebrovascular	• Excluded those with a prior history of cardiovascular disease

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
						disease • Incidence of death from pulmonary embolism	
MARADIT-KREMERS 2012	1905 with psoriasis	Rochester Epidemiology Project – psoriasis treated with systemic therapy or phototherapy	Rochester Epidemiology Project – psoriasis not treated with systemic therapy or phototherapy	MN, USA	Mean 6.3 ± 3.5 years	• Incidence of cardiovascular disease (composite of myocardial infarction, revascularisation, cerebrocascular events, heart failure and cardiovascular death)	• Few participants in each treatment subgroup
MEHTA 2010	17933 (3603 with psoriasis)	GPRD – severe psoriasis (psoriasis diagnostic code and history of systemic therapy)	GPRD – no psoriasis diagnostic codes (matched by practice, index date and date of registration)	UK	Mean: 3.40 ± 2.8 years for non-psoriasis and 3.4 ±2.7 years for psoriasis group	• Incidence of death	• Same cohort as ABUABARA2010 and MEHTA2011
MEHTA 2011	17933 (3603 with psoriasis)	GPRD – severe psoriasis (psoriasis diagnostic code and history of systemic therapy)	GPRD – no psoriasis diagnostic codes (matched by practice, index date and date of registration)	UK	Mean 3.4 ± 2.8 years for non-psoriasis and 3.4 ± 2.7 years for psoriasis group	• Incidence of first major adverse cardiac event (nonfatal myocardial infarction, nonfatal stroke or death due to	• Same cohort as ABUABARA2010 and MEHTA2010 • Disease severity classified according to systematic treatments (potential misclassification if prescribed for another indication) • Excluded those with history of

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
						cardiovascular cause)	cardiovascular disease, defined as ischemic heart disease, myocardial infarction, transient ischaemic attack, stroke or peripheral arterial disease on or before the start date
OLSEN 1992	6910 with psoriasis	Danish National Hospital Discharge Register – diagnosis of psoriasis (ICD codes)	Danish national population	Denmark	Mean 5.1 years , maximum 11 years	• Incidence of cancers	
POIKOLAINAN 1999	5687 with psoriasis	Finnish hospital discharge register – psoriasis as the main diagnosis	Entire Finnish population	Finland	Mean almost 14 years	• Incidence of death	
PRIZMENT 2011	33,266 (719 with psoriasis)	Iowa Women's Health Study – 2+ psoriasis claims from any Medicare file or 1+ psoriasis claim from a dermatologist	Iowa Women's Health Study – no psoriasis diagnostic code	Iowa, USA	2-15 years	• Incidence of cancer	• Only included women over 65 years • Confounders mainly measured in 1986 but follow-up started in 1991 • Stratified by psoriasis severity
QURESHI 2009	78061 (1813 with psoriasis)	Registered nurses reporting psoriasis	Registered nurses not reporting psoriasis	USA	14 years	• Incidence of diabetes • Incidence of hypertension	• Excluded women with diabetes or hypertension • Women only and predominantly white • Did not have any data on therapies
SHU 2011	1013503	Swedish hospital	Swedish	Sweden	Unclear	• Incidence of cancer	• Limited to those already known to

Reference	Number of participants (number with psoriasis)	Exposed cohort	Unexposed cohort	Location	Mean follow-up period (years)	Outcomes	Notes
	(1746 with psoriasis)	discharge registry – psoriasis diagnosis according to ICD	hospital discharge registry – no psoriasis diagnosis according to ICD			mortality	have experienced primary neoplasm, and compares risk of death due to cancer in those with and without psoriasis • Subgroup data for disease severity, age and alcohol use
WAKKEE 2010	43397 (15,820 with psoriasis)	PHARMO record linkage system – hospital discharge diagnosis of psoriasis/PsA or use of psoralen, calcipotriol, calcitriol, dithranol, fumaric acids and/or efalizumab	PHARMO record linkage system – no likelihood of having psoriasis (matched on age and sex)	Netherlands	Median follow-up 6 years	• Incidence of (hospitalisation for) ischaemic heart disease • Incidence of acute myocardial infarction	• Excluded if hospitalised for skin conditions other than psoriasis, or had <6 months history before start of follow-up (which is twice the maximum prescription time allowed in the Netherlands) • Excluded those with HIV, immune disorders, inflammatory bowel diseases, hepatitis B and C, multiple sclerosis, rheumatoid arthritis, and status after organ transplant

Due to the design of the studies considered, GRADE could not be used to assess quality. Therefore, quality was assessed using a modified version of the Checklist for Prognostic Studies (NICE Guidelines Manual, 2009) (seeTable 29). The quality rating was derived by assessing the risk of bias across 5 domains (selection bias; attrition bias; prognostic factor bias; outcome bias; and confounders and analysis bias) and although listed per study the adequacy of outcome measurement and controlling for confounders were considered per outcome; however, the rating was the same across outcomes unless otherwise stated. Note that very few of the studies reported how missing data were handled or if imputation was used.

Table 29: Study quality checklist

Reference	Quality assessment – study methodology								
	Prospective	Representative population	Minimal attrition bias	Prognostic factor	Outcomes adequately	Confounders accounted	Exposed/non-exposed from	Appropriate statistical	Quality

Reference	Quality assessment – study methodology								
		sample		measured appropriately	measured	for[(a)]	the same cohort	analysis	
ABUABARA 2010	×	✓	?	✓	✓	~	✓	✓	VERY LOW
ABUABARA 2011	×	✓	?	✓	✓	~	✓	✓	VERY LOW
AHLEHOFF 2011	×	✓	?	✓	✓	~	✓	✓	MODERATE
AHLEHOFF 2011B	×	✓ (but only those known to have had MI)	✓	✓	✓	~	✓	✓	MODERATE
AHLEHOFF 2011D	×	✓	?	✓	✓	~	✓	✓	MODERATE
AHLEHOFF 2011E	×	✓	✓	✓	✓	~	✓	✓	MODERATE
BOFFETTA 2001	×	✓	?	✓	✓	~	×	×	VERY LOW
BRAUCHLI 2008	×	✓	?	✓	✓	~	✓	×	VERY LOW
BRAUCHLI 2009	×	✓	?	✓	✓	~	✓	×	VERY LOW
BRAUCHLI 2009A	×	✓	?	✓	✓	~	✓	×	VERY LOW
CHEN2011	×	✓	?	✓	✓	~	✓	✓	LOW
FRENTZ1999	×	✓	✓	✓	✓	~	×	×	VERY LOW
GELFAND2003	×	✓	×	✓	✓	~	✓	✓	LOW

Reference	Quality assessment – study methodology								
GELFAND2006	×	✓	?	✓	✓	~	✓	✓	LOW
GELFAND2006A	✓	✓	?	✓	✓	~	✓	✓	VERY LOW
GELFAND2007	×	✓	?	✓	✓	~	✓	✓	Mild psoriasis: LOW Severe psoriasis: MODERATE
GELFAND2009	×	✓	?	✓	✓	~	✓	✓	MODERATE
HANNUKSELASVHAN2000	×	✓	?	✓	✓	~	×	×	VERY LOW
JI2009	×	✓	?	✓	✓	~	✓	×	VERY LOW
KAYE2008	×	✓	?	✓	✓	~	✓	✓	VERY LOW
KURD2010	×	✓	?	✓	✓	~	✓	✓	MODERATE
LI2011	×/✓ (B)	×	✓	✓ (self-report but validated tools)	✓ (self-report but validated tools)	~	✓	✓	MODERATE
LIN2011	×	✓	?	✓	✓	~	✓	✓	MODERATE
MALLBRIS2004	×	✓	?	✓	✓	~	×	×	VERY LOW
MARADIT-KREMERS2012	×	×	?	✓	✓	~	✓	✓	LOW

Reference	Quality assessment – study methodology								
MEHTA2010	×	✓	?	✓	✓	~	✓	✓	MODERATE
MEHTA2011	×	✓	?	✓	✓	~	✓	✓	MODERATE
OLSEN1992	×	✓	✓	✓	✓	~	×	×	VERY LOW
POIKOLAINAN1999	×	✓	?	✓	✓	~	×	×	VERY LOW
PRIZMENT2011	×/✓ (B)	×	?	✓	✓	~	✓	✓	LOW
QURESHI2009	✓	×	?	✓ (self-report but validated tools)	✓ (self-report but validated tools)	~	✓	✓	MODERATE
SHU2011	×	✓ (but only those known to have cancer)	✓	✓	✓	~	✓	✓	MODERATE
WAKKEE2010	×	✓	?	✓	✓	~	✓	✓	LOW

×: No
✓: Yes
?: Not reported
(a) See tables 26-32 for details of controlling of confounders.
(b) This study had both retrospective and prospective elements to its design
MI: Myocardial infarction

7.17.1.3 Confounding variables

In observational studies it is necessary to control or adjust for confounding variables, other than the prognostic factor being investigated, that may also affect the observed outcomes. Therefore, in assessing study quality the adequacy of controlling for confounders was assessed for each outcome.

1 Table 30-Table 36 summarise which of the key confounders have been controlled for and by what method in each of the included studies.

2 **Table 30: Adequacy of controlling for key confounders – cardiovascular disease**

Study	Age	Sex	Smoking	Alcohol excess	BMI/obesity	Hyperlipidaemia	Hypertension	Diabetes	Calendar time	Other	Excluded
AHLEHOFF 2011	✓(a/b)	✓(a)	×(c)	×	✓(a)	×	×	✓(a)	✓(a)	✓(d)	✓(e)
AHLEHOFF 2011D	✓(a/b)	✓(a)	×(c)	×	×(c)	×	×	✓(a)	✓(a)	✓(d)	✓(e)
AHLEHOFF 2011E	✓(a/b)	✓(a)	×(c)	×	×(c)	×	×	✓(a)	✓(a)	✓(d)	✓(e)
AHLEHOFF 2011B	✓(a)	✓(a)	×(c)	×	×(c)	×	×	✓(a)	✓(a)	✓(d)	✓(e)
ABUABARA2011	✓(a)	✓(a)	×	×	×	✓(a)	✓(a)	✓(a)	×	✓(f)	×(g)
BRAUCHLI 2009A	✓(h)	✓(h)	×	×	×	×	×	×	✓(h)	×	✓(e)
GELFAND 2006A	✓(a)	✓(a)	✓(a)	×	×(i)	✓(a)	✓(a)	✓(a)	✓(j)	×	×(j)
GELFAND 2009	✓(a)	✓(a)	✓(a)	×	×(k)	✓(a)	✓(a)	✓(a)	×	✓(l)	×(m)
KAYE 2008	✓(h)	✓(h)	×	×	×	×	×	×	✓(h)	×	×
LIN 2011	✓(b)	✓(b)	×	✓	×	✓(n)	✓(n)	✓(n)	×	✓(o)	✓(e)
MALLBRIS 2004	✓(a/b)	✓(a/b)	×	×	×	×	×	×	✓(a)	×	✓(e)

Study	Age	Sex	Smoking	Alcohol excess	BMI/obesity	Hyperlipidaemia	Hypertension	Diabetes	Calendar time	Other	Excluded
MARADIT-KREMERS 2012	✓(a)	✓(a)	✗	✗	✓(a)	✓(a)	✓(a)	✓(a)	✗	✓(p)	✓(e)
MEHTA 2010	✓(a)	✓(a)	✓(a)	✗	✓(a)	✓(a)	✓(a)	✓(a)	✗	✗	NA
MEHTA 2011	✓(a)	✓(a)	✓(a)	✗	✓(a)	✓(a)	✓(a)	✓(a)	✗	✗	✓(e)
WAKKEE 2010	✓(a)	✓(a)	✗	✗	✗	✓(a)	✓(a)	✓(a)	✗	✓(q)	✗

✗ *Not controlled for*
✓ *Controlled for*

(a) Adjusted for the confounder in statistical analyses
(b) Stratified for this variable
(c) Adjusts for this surrogate markers for smoking and obesity
(d) Valvular heart disease, Charlson Index (defined by 19 prespecified diagnoses up to 1-year before study entry, modified to ICD-10;), socioeconomic data and medication
(e) Excluded patients with outcome of interest at inclusion (prevalent disease)
(f) Depression, history of MI
(g) Sensitivity analysis showed that excluding those with prevalent MI did not substantially alter the effect size
(h) Matched on the confounder
(i) BMI adjusted for in a sensitivity analysis including only the 40% with data available for this covariate; the effect estimate was reduced effect considerably (although the difference compared to the unexposed cohort was still significant for both mild and severe psoriasis)
(j) MI had to be subsequent to psoriasis diagnosis
(k) Obesity not included as it did not alter the association between psoriasis and stroke
(l) Atrial fibrillation
(m) Sensitivity analysis showed that excluding those with prevalent stroke or TIA did not alter the effect size
(n) Other cardiac diseases, affective disorders, epilepsy, ischaemic heart disease, use of non-steroidal anti-inflammatory drugs or acetylasalicyclic acid.
(o) Adjustments made for hospital cluster, monthly income, geographic region and urbanisation level.
(p) Cholesterol and blood pressure
(q) Healthcare consumption proxy and metabolic drugs

Table 31: Adequacy of controlling for key confounders – venous thromboembolism and pulmonary embolism

Study	Age	Sex	Smoking	Alcohol excess	BMI/obesity	Hyperlipidaemia	Hypertension	Diabetes	Calendar time	Recent surgery	Sepsis	Immobility or hospital admission	Excluded
AHLEHOFF 2011	✓(a/b)	✓(a)	✗(c)	✗	✓(a)	✗	✗	✓(a)	✓(a)	✗	✗	✗	✓(e)
MALLBRIS 2004	✓(a/b)	✓(a/b)	✗	✗	✗	✗	✗	✗	✓(a)	✗	✗	✗	✓(e)

✗ *Not controlled for*
✓ *Controlled for*
(a) Adjusted for the confounder in statistical analyses
(b) Stratified for this variable
(c) Adjusts for this surrogate markers for smoking and obesity
(d) Valvular heart disease, Charlson Index (defined by 19 prespecified diagnoses up to 1-year before study entry, modified to ICD-10;), socioeconomic data and medication
(e) Excluded patients with outcome of interest at inclusion (prevalent disease)

Table 32: Adequacy of controlling for key confounders – alcohol and smoking-related disease

Study	Confounder								
	Age	Sex	BMI/ obesity	Hyperlipidaemia	Hypertension	Diabetes	Other	Calendar time	Excluded[a]
POIKOLAINAN 1999	✓[b]	✓[b]	×	×	×	×	×	✓[b]	×

× *Not controlled for*
✓ *Controlled for*
(a) Excluded patients with disease of interest
(b) Matched on the confounder

Table 33: Adequacy of controlling for key confounders – diabetes and hypertension

Study	Confounder										
	Age	Sex	Smoking	BMI/obesity	Hyperlipidaemia	Hypertension	Diabetes	Alcohol intake	Physical activity	Calendar time	Excluded
BRAUCHLI2008	✓ [a]	✓ [a]	×	×	×	×	×	×	×	✓ [a]	✓ [b]
LI2011	✓[c]	✓[a]	✓[c]	✓[c]	✓[c]	✓[c]	× (controlled for family history)	✓[c]	✓[c]	×	✓ [b]
QURESHI 2009	✓[c]	✓[a]	✓[c]	✓[c]	×	NA	NA	✓[c]	✓[c]	✓ [a]	✓ [b]

× *Not controlled for*
✓ *Controlled for*
? Unclear
(a) Matched on the confounder
(b) Those with diabetes or hypertension at baseline were excluded
(c) Adjusted for the confounder in statistical analyses

Table 34: Adequacy of controlling for key confounders – depression

Study	Confounder									
	Age	Sex	Treatment	Diabetes	Hypertension	Hyperlipidaemia	Cancer	BMI	Calendar time	Excluded[a]

Study	Confounder									
KURD 2010	✓ (b	✓(b)	✓ (c)	✓ (c)	✓ (c)	✓ (c)	✓ (c)	✓ (c)	×	×

× *Not controlled for*
✓ *Controlled for*

(a) Excluded patients with outcome of interest at inclusion (prevalent disease)
(b) Adjusted for the confounder in statistical analyses
(c) Results robust to sensitivity analysis for incident cases only, retinoids, diagnosis of psoriatic arthropathy to capture severe skin phenotype, treated with psoralen or phototherapy, analysis controlling for diabetes, hypertension, hyperlipidaemia, cancer and BMI

Table 35: Adequacy of controlling for key confounders – cancer

Study	Confounder									
	Age	Sex	Smoking	Alcohol	Liver cirrhosis	Calendar time	Sun exposure	Skin type	Treatments	Excluded[(a)]
BOFFETTA2001	✓ (b)	✓ (b)	×	×	×	✓ (a)	×	×	×	✓
BRAUCHLI2009	✓ (c)	✓ (c)	×	×	×	×	×	×	×	✓
CHEN2011	✓ (c)	✓ (c)	×	×	×	×	×	×	✓ (d)	✓
FRENTZ1999	✓ (c)	✓ (c)	×	×	×	×	×	×	×	×
GELFAND2003	✓ (d)	✓ (d)	×	×	×	×	×	×	× (e)	✓
GELFAND2006	✓ (d)	✓ (d)	×	×	×	×	×	×	×	× (f)
HANNUKSELASVHAN2000	✓ (g)	✓ (g)	×	×	×	×	×	×	×	×
JI2009	✓ (h)	✓ (h)	×	×	×	×	×	×	×	?
OLSEN1992	✓(c)	✓ (c)	×	×	×	✓ (h)	×	×	×	×
PRIZMENT2011	✓ (c)	✓ (i)	✓ (c)	×	×	×	×	×	×	✓
SHU2011	✓ (c)	✓ (c)	× (j)	× (k)	×	✓ (c)	×	×	×	NA

× *Not controlled for*
✓ *Controlled for*

(a) Excluded patients with outcome of interest at inclusion (prevalent disease)
(b) Multiplied the gender, 5 year age group and calendar year specific incidence rates by the person-year distribution of the cohort
(c) Adjusted for the confounder in statistical analyses
(d) Stratified for this variable
(e) Sensitivity analysis showed that excluding patients treated with methotrexate did not alter the effect meaningfully
(f) Sensitivity analysis showed that excluding patients treated with prior lymphoma did not attenuate the association
(g) Standardised incidence ratios were calculated by dividing the number of cases by the expected cases, which were based on the national sex-specific and age-specific cancer incidence rates
(h) Expected numbers were calculated using the incidence rates for all individuals without a history of psoriasis, and the rates were standardised by 5-year age, gender, period (5 years group), socioeconomic status and residential status. For cancers of the female reproductive system, rates were also standardised for age at first childbirth and parity
(i) Matched on the confounder
(j) Chronic obstructive pulmonary disease, as a surrogate for smoking, was found not to influence the effect size and so was not included in the final model
(k) Alcohol-related disorders, as a surrogate for alcohol use, was found not to influence the effect size and so was not included in the final model

Table 36: Adequacy of controlling for key confounders – mortality

Study	Confounder									
	Age	Sex	Treatment	Diabetes	Hypertension	Hyperlipidaemia	Cancer	BMI	Calendar time	Other
ABUABARA2010	✓ (a)	✓(a)	×	×	×	×	×	×	×	×
GELFAND2007	✓ (a)	✓(a)	×	×	×	×	×	×	×	✓(b)

× *Not controlled for*
✓ *Controlled for*
(a) Adjusted for the confounder in statistical analyses
(b) Sensitivity analysis for psoriatic arthritis; rheumatologic diseases; person-time starts with first diagnosis of psoriasis during 'up to standard' time; index date; treated with methotrexate sodium, treated with methotrexate; prescribed an oral retinoid in severe psoriasis subgroup only.

It is not appropriate to pool the results of observational studies owing to inconsistencies in design and comparison, as well as the potential confounders. Therefore, all observational study data have been considered individually.

7.17.1.4 Summary statistics

In the included studies a range of summary statistics are used, some of which are specific to prognostic investigations. To aid interpretation, a summary of the definitions of these statistics is provided inTable 37. Note that the absolute risks, where available, are also provided in Appendix Q.

Table 37: Defining summary statistics

Summary statistic	Definition
Incidence rate	Incident cases divided by the number in the cohort multiplied by the exposure time
Standardised incidence/rate ratio (SIR/SRR) Standardised morbidity ratio (SMR) Incidence rate ratio (IRR)	Incidence rate observed among exposed divided by the incidence rate expected in a matched population
Hazard ratio	A hazard measures instantaneous risk and may change continuously A hazard ratio describes how many times more (or less) likely a participant is to have the event at a particular point in time in one group compared to another

7.17.2 Cardiovascular disease

7.17.2.1 Incidence of cardiovascular disease and mortality compared to the general population

Seventeen population-based cohort studies investigated the incidence of cardiovascular diseases and death from cardiovascular diseases.

Three population-based cohort studies used the same cohort taken from the General Practice Research Database (GPRD) comparing patients with severe psoriasis with the people without psoriasis from the same database[116,130,139]. One[116] investigated the cause-specific risk of mortality, and adjusted for age and sex; another [130] investigated the risk of cardiovascular/cerebrovascular disease mortality, with the unexposed group being matched on practice, date of registration and psoriasis index date and adjusting for age, sex, hypertension, hyperlipidaemia, history of diabetes, and smoking (current versus never and former versus never); and the final study[139] assessed the risk of a first major adverse cardiac event, again adjusting for age, sex, hypertension, hyperlipidaemia, diabetes, smoking (current versus never and former versus never) and also BMI.

Four more studies also sampled from the GPRD. One cohort study [6] investigated the risk factors for myocardial infarction (MI) and other vascular diseases in patients with psoriasis compared to patients without psoriasis. They reported the incidence of diabetes, hypertension, obesity, hyperlipidaemia, MI, atherosclerosis, peripheral vascular disease and stroke. They matched cohorts by year of birth, sex, general practice and index date. One prospective study[124] investigated the incidence of acute MI. They adjusted for age, sex, diabetes, hyperlipidaemia, hypertension and current smoking. An inception cohort study[120] assessed the risk of MI, stroke and transient ischaemic attack. They adjusted for age, sex and calendar time by matching. Another cohort study[125] investigated the risk of stroke in patients with mild or severe psoriasis compared to patients without psoriasis who were matched on practice, date of registration in the practice and the psoriasis index date to ensure they were assessed by similar physicians during the same time period.

Four further population-based cohort studies were sampled from the entire Danish adult population, and included very similar samples, varying only according to certain specific exclusion criteria, and all were adjusted for age, calendar year, concomitant medication, gender, socioeconomic data and comorbidity (assessed by the Charlson index)[140-143]. The outcomes they assessed were venous thromboembolism/pulmonary embolism[142], all-cause mortality, cardiovascular mortality and hospitalisations for MI and coronary revascularisation[143]; ischemic stroke[141]; all-cause mortality; and a composite of recurrent MI, stroke and cardiovascular death among those known to have had a first-time MI[140]. Three of the studies only included new-onset psoriasis and gave stratified data for different age groups and for mild and severe psoriasis[141,142 143], while one was a small cohort of only those with first-time MI, investigating the subsequent risk of death and further cardiovascular events[140].

Two population-based cohort studies[117,129] used the Swedish Inpatient Registry to investigate cardiovascular mortality. One reported on hospital in- and out-patients with psoriasis compared to the general population using the death registry and registry of population and population changes[129]. The outpatient cohort had a wide range of patients with varying disease severity but the authors state that most had either mild psoriasis or psoriasis controlled by outpatient treatment. They also reported the incidence of death specifically from ischaemic heart disease and pulmonary embolism. Another reported on people hospitalised specifically for psoriasis and reported standardised mortality ratios for cardiovascular disease in general, as well as specifically for ischaemic heart disease, cerebrovascular disease and arterial diseases[117].

One cohort study[133] using the Dutch hospital and pharmacy-linked medical databases (PHARMO record linkage system) investigated acute ischemic heart disease. They included people with psoriasis and people without psoriasis matched for age, gender and presence of a database record within 30 days of the cohort entry of a psoriasis patient. They were further adjusted for the healthcare consumption proxy, metabolic drugs and an interaction term between psoriasis and healthcare consumption.

Another population-based cohort[128] looked at the risk of acute MI in the Longitudinal Health Insurance Database in Taiwan in people with and without psoriasis. They were stratified by age and

sex and adjusted for hospital clustering, monthly income, level of urbanisation, geographic location of the community in which the patient lived, hypertension, diabetes and hyperlipidaemia.

Two cohort studies addressed the risk of cardiovascular disease among people with psoriasis treated with systemic therapies and phototherapy. One study[144] compared the incidence of acute myocardial infarction in the two treatment groups using data from a US medical and pharmacy claims database, while the other[145] compared the incidence of a composite outcome of cardiovascular events in each of the treatment groups with that in people with psoriasis not exposed to that intervention using data from medical care providers in Olmsted County, MN, USA.

7.17.2.2 Evidence summary

Table 38: Incidence of cardiovascular disease and risk of cardiovascular mortality in people with psoriasis compared with people without psoriasis

Outcome	Study	Multivariate adjusted risk estimate (95% CI)		
		All psoriasis patients	Mild psoriasis patients	Severe psoriasis patients
CVD mortality	ABUABARA 2010 & MEHTA2010	-	-	HR 1.57 (1.26-1.96)[a]
	MALLBRIS 2004		SMR 0.94 (0.89-0.99)[b]	SMR 1.52 (1.44-1.60)[b]
	AHLEHOFF 2011D		IRR 1.14 (1.06-1.22)	IRR 1.57 (1.27-1.94)
	BOFFETTA2001			SMR 1.45 (1.35-1.56)[c]
Cerebrovascular disease mortality	MALLBRIS 2004			SMR 1.63 (1.47-1.80)
	BOFFETTA2001			SMR 1.33 (1.11-1.59)[c]
Atherosclerosis[d]	KAYE2008	HR 1.28 (1.10-1.48)	-	-
Angina	KAYE2008	HR 1.20 (1.12-1.29)	-	-
Peripheral vascular disease	KAYE2008	HR 1.29 (1.13-1.47)	-	-
Arterial disease mortality	BOFFETTA2001			SMR 1.34 (0.97-1.80)[c]
Ischaemic heart disease	WAKKEE 2010	HR 1.05 (0.95-1.17)	-	-
Ischaemic heart disease *mortality*	MALLBRIS 2004	-	-	SMR 1.86 (1.76-1.96)
	BOFFETTA2001			SMR 1.55 (1.42-1.70)[c]
Myocardial infarction	BRAUCHLI 2009A	IRR 1.07 (0.89-1.29)	-	
	KAYE2008	HR 1.21 (1.10-1.32)	-	-
	LIN2011	HR 2.10 (1.27-3.43), p<0.01	-	-
	GELFAND 2006A	-	HR Age 30: 1.29 (1.14-	HR Age 30: 3.10 (1.98-

	Study	Multivariate adjusted risk estimate (95% CI)		
			1.46) Age 60: 1.08 (1.03-1.13)	4.86) Age 60: 1.36 (1.13-1.64)
	AHLEHOFF 2011D		IRR 1.22 (1.12-1.33)	IRR 1.45 (1.10-1.9)
	WAKKEE 2010	HR 0.94 (0.80-1.11)		
All cause *mortality* following first-time MI	AHLEHOFF 2011B	HR 1.18 (0.97-1.43)	-	-
Composite of stroke, recurrent MI and CVD mortality following first-time MI	AHLEHOFF 2011B	HR 1.26 (1.06-1.54)	-	-
Transient ischaemic attack	BRAUCHLI 2009A	IRR 0.98 (0.81-1.19)	-	-
Stroke	BRAUCHLI 2009A	IRR 0.92 (0.77-1.09)	-	-
	GELFAND 2009	-	HR 1.06 (1.01-1.11)	HR 1.43 (1.10-1.87)
	KAYE 2008	HR 1.12 (1.00-1.25)	-	-
	AHLEHOFF 2011D		IRR 1.25 (1.16-1.33)	IRR 1.71 (1.39-2.11)
Ischaemic stroke	AHLEHOFF 2011E	-	IRR 1.25 (1.17-1.34)	IRR 1.65 (1.33-2.05)
Venous thromboembolism	AHLEHOFF 2011	-	IRR 1.35 (1.21-1.49)	IRR 2.06 (1.63-2.61)
Pulmonary embolism	AHLEHOFF 2011	-	IRR 1.14 (0.95-1.37)	IRR 1.88 (1.22-2.89)
Pulmonary embolism *mortality*	MALLBRIS 2004			SMR 1.64 (1.12-2.31)
Coronary revascularisation	AHLEHOFF 2011D	-	IRR 1.37 (1.26-1.49)	IRR 1.77 (1.35-2.32)
Composite of stroke, MI and CVD mortality	AHLEHOFF 2011D	-	IRR 1.2 (1.14-1.25)	IRR 1.58 (1.36-1.82)
Major adverse cardiac events	MEHTA2011	HR 1.53 (1.26-1.85)		

(a) Outpatients who were classified as having severe psoriasis
(b) Outpatients. The study did not classify these patients as having mild psoriasis but we have categorised it as such
(c) Patients who were hospitalised at least once. The study did not classify these patients as having severe psoriasis but we have categorised it as such
(d) Atherosclerosis was not defined.
HR: Hazard ratio
IRR: Incidence rate ratio

SMR: Standardised morbidity/mortality ratio

7.17.2.3 Evidence statements

The risk of mortality from cardiovascular disease or cerebrovascular disease was statistically significantly higher for those with severe psoriasis compared to an unexposed cohort [4 studies; 4,096,711 participants (44,745 with severe psoriasis); very low to moderate quality evidence][117,129,130,143]. One study also showed a statistically significantly higher risk of mortality from cardiovascular disease in mild psoriasis, although the effect was larger in the severe group [1 study; 4,040,257 participants (34,371 with mild psoriasis); moderate quality evidence][143]; however, another study suggested that the risk was statistically significantly lower in people with mild psoriasis compared with the unexposed cohort) [1 study; 28,748 people with psoriasis); very low quality evidence][129].

The incidence of major adverse cardiac events was statistically significantly higher for those with psoriasis compared to an unexposed cohort [1 study; 17933 participants (3603 with psoriasis); moderate quality evidence][139].

The incidence of atherosclerosis and angina were statistically significantly higher for those with psoriasis compared to an unexposed cohort [1 study; 263,948 participants (44,164 with psoriasis); very low quality evidence][6].

The incidence of peripheral vascular disease was statistically significantly higher for those with psoriasis compared to an unexposed cohort [1 study; 263,948 participants (44,164 with psoriasis); very low quality evidence][6]. However, there was no significant difference in the incidence of death from arterial diseases [1 study; 9773 people with psoriasis; very low quality evidence][117].

The incidence of venous thromboembolism was statistically significantly higher for those with psoriasis (mild and severe) compared to an unexposed cohort [1 study; 4164739 participants (38,664 with psoriasis); moderate quality evidence] [142]; however, more specifically, pulmonary embolism and death from pulmonary embolism was only statistically significantly higher for those with severe psoriasis [2 studies; 67,412 people with psoriasis; very low to moderate quality evidence][129,142].

The risk of ischaemic heart disease and death from ischaemic heart disease was statistically significantly higher for those with severe psoriasis but not for a mixed psoriasis severity population compared to the general population [3 studies; 81,918 people with psoriasis; low to very low quality evidence][117,129,133].

The risk of myocardial infarction was statistically significantly higher for those with psoriasis (mild and severe) compared to an unexposed cohort [4 studies; 5,251,564 participants (239,105 with psoriasis); very low to moderate quality evidence][6,124,128,143] but was not statistically significantly different in 2 studies [114,801 participants (52,522 with psoriasis);low to very low quality evidence; low to very low quality evidence][120,133].

Following first-time MI, the risk of subsequent all-cause mortality was not statistically significantly higher among those with psoriasis, while the composite risk of stroke, recurrent MI and CVD mortality was statistically significantly higher in the psoriasis cohort compared with the general population following first-time MI [1 study; 49397 participants (462 with psoriasis); moderate quality evidence][140].

The incidence of transient ischaemic attack was not statistically significantly different between people with and without psoriasis [1 study; 73,404 participants (36,702 with psoriasis); very low quality evidence][120].

The risk of stroke/ischaemic stroke was statistically significantly higher for those with psoriasis (mild and severe) compared to an unexposed cohort [4 studies; 120,424 people with psoriasis; very low to moderate quality evidence][6,120,141,143] but there was no statistically significant difference in one study [1 study; 643,729 participants (132,746 with psoriasis); moderate quality evidence][125].

The incidence of coronary revascularisation was statistically significantly higher for those with psoriasis (mild and severe) compared to an unexposed cohort [1 study; 4,040,257 participants (36,992 with psoriasis); moderate quality evidence][143].

The composite outcome of stroke, MI and CVD mortality risk was statistically significantly higher for those with psoriasis (mild and severe) compared to an unexposed cohort [1 study; 4,040,257 participants (36,992 with psoriasis); moderate quality evidence][143].

7.17.3 Cardiovascular disease risk modification factors

In addition to stratifying for disease severity, some studies gave information for different subgroups.

7.17.3.1 Age

Evidence summary

Seven studies[120,124,129,130,141-143]provided data regarding the relative risk of cardiovascular disease in the psoriasis population compared with the general population or people without psoriasis for different age subgroups.

Table 39: Incidence of cardiovascular disease and risk of cardiovascular mortality in people with psoriasis compared with the general population or people without psoriasis stratified by age

Outcome	Study	Multivariate adjusted risk estimate (95% CI)		
		All psoriasis patients	Mild psoriasis patients	Severe psoriasis patients
CVD mortality	MALLBRIS2004 (stratified by age at first hospital admission)		SMR[(a)] **0-19:** 0.00 (0.00-20.3) **20-39:** 0.65 (0.26-1.34) **40-59:** 1.00 (0.85-1.16) **60+:** 0.93 (0.88-0.99)	SMR[(b)] **0-19**: 0.00 (0.00-3.74) **20-39**: 2.62 (1.91-3.49) **40-59**: 1.91 (1.74-2.09) **60+**: 1.37 (1.29-1.46) p-value for trend <0.001
	AHLEHOFF2011D		IRR **18-50 years:** 1 (0.66-1.50) **51-70 years:** 1.2 (1.05-1.36) **>70 years:** 1.14 (1.06-1.24)	IRR **18-50 years:** 2.98 (1.32-6.73) **51-70 years:** 2.22 (1.59-3.10) **>70 years:** 1.18 (0.89-1.57)
Cerebrovascul	MALLBRIS200			SMR[(B)]

	Study	Multivariate adjusted risk estimate (95% CI)		
ar disease mortality	4			**20-39 years:** 1.85 (0.68-4.02) **40-59 years:** 1.92 (1.52-2.40) **60+ years:** 1.56 (1.38-1.75)
Ischaemic heart disease mortality	MALLBRIS2004	-	-	SMR **20-39 years:** 2.91 (1.98-4.14) **40-59 years:** 2.22 (2.00-2.46) **60+ years:** 1.71 (1.60-1.83)
Myocardial infarction	BRAUCHLI2009A	IRR **Age 0-29:** NA **Age 30-59:** 1.99 (1.37-2.88) **Age 60-80+:** 0.92 (0.75-1.14)	-	
	GELFAND2006A	-	HR **30 years:** 1.29 (1.14-1.46) **60 years:** 1.08 (1.03-1.13)	HR **30 years:** 3.10 (1.98-4.86) **60 years:** 1.36 (1.13-1.64)
	AHLEHOFF2011D		IRR **18-50 years:** 1.17 (0.89-1.54) **51-70 years:** 1.12 (0.99-1.26) **>70 years:** 1.3 (1.16-1.45)	IRR **18-50 years:** 2.32 (1.19-4.50) **51-70 years:** 1.44 (0.99-2.09) **>70 years:** 1.00 (0.63-1.45)
Transient ischaemic attack	BRAUCHLI2009A	IRR **Age 0-29:** NA **Age 30-59:** 1.14 (0.66-1.97) **Age 60-80+:** 0.99 (0.80-1.22)	-	-
Stroke	BRAUCHLI2009A	IRR **Age 0-29:** NA **Age 30-59:** 0.75 (0.49-1.16) **Age 60-80+:** 0.98 (0.81-1.18)	-	-
	AHLEHOFF201		IRR	IRR

	Study	Multivariate adjusted risk estimate (95% CI)		
	1D		**18-50 years:** 1.61 (1.32-1.97) **51-70 years:** 1.22 (1.10-1.35) **>70 years:** 1.15 (1.05-1.20)	**18-50 years:** 1.64 (0.88-3.07) **51-70 years:** 1.87 (1.41-2.49) **>70 years:** 1.47 (1.07-1.26)
Ischaemic stroke	AHLEHOFF2011E	-	IRR **18-50 years:** 1.97 (1.66-2.34) **≥50 years:** 1.13 (1.04-1.21)	IRR **18-50 years:** 2.80 (1.81-4.34) **≥50 years:** 1.34 (1.04-1.71)
Venous thromboembolism	AHLEHOFF2011	-	IRR **<50 years:** 1.24 (0.97-1.58) **≥50 years:** 1.26 (1.13-1.42)	IRR **<50 years:** 3.14 (1.98-4.97) **≥50 years:** 1.74 (1.32-2.28)
Pulmonary embolism mortality	MALLBRIS2004 (stratified by age at first hospitalisation)			SIR **20-39 years:** 5.18 (0.63-18.7) **40-59 years:** 2.24 (1.07-4.12) **60+ years:** 1.36 (0.83-2.11)
Coronary revascularisation	AHLEHOFF2011D	-	IRR **18-50 years:** 1.62 (1.26-2.07) **51-70 years:** 1.26 (1.13-1.40) **>70 years:** 1.45 (1.24-1.69)	IRR **18-50 years:** 2.27 (1.17-4.42) **51-70 years:** 1.63 (1.16-2.27) **>70 years:** 1.58 (0.92-1.45)
Composite of stroke, MI and CVD mortality	AHLEHOFF2011D	-	IRR **18-50 years:** 1.4 (1.20-1.63) **51-70 years:** 1.21 (1.12-1.29) **>70 years:** 1.16 (1.09-1.24)	IRR **18-50 years:** 2.04 (1.35-3.09) **51-70 years:** 1.85 (1.51-2.26) **>70 years:** 1.19 (0.95-1.50)

1 *(a) Outpatients. The study did not classify these patients as having mild psoriasis but we have categorised it as such*
2 *(b) Patients who were hospitalised at least once. The study did not classify these patients as having severe psoriasis but we*
3 *have categorised it as such*
4 HR: Hazard ratio
5 IRR: Incidence rate ratio
6 SMR: Standardised morbidity/mortality ratio

7 **Evidence statements**

8 In people with severe psoriasis there was a trend towards the risk compared with the general
9 population or people without psoriasis being greater among those in younger age groups (i.e.,
10 decreasing risk attributable to psoriasis as age increased) for:

- Cardiovascular/cerebrovascular disease mortality [2 studies; 31,369 people with severe psoriasis; very low to moderate quality evidence][129,143]
- Mortality from ischaemic heart disease [1 study; 28748 people with severe psoriasis; very low quality evidence][129]
- Myocardial infarction [2 studies; 6458 people with severe psoriasis; very low to moderate quality evidence][124,143]
- Stroke [1 study; 2621 people with severe psoriasis; moderate quality evidence][143]
- Ischaemic stroke [1 study; 2793 people with severe psoriasis; moderate quality evidence][141]
- Venous thromboembolism [1 study; 3526 people with severe psoriasis; moderate quality evidence][142]
- Mortality from pulmonary embolism [1 study; 28748 people with severe psoriasis; very low quality evidence][129]
- Coronary revascularisation [1 study; 2621 people with severe psoriasis; moderate quality evidence][143]
- Composite of stroke, myocardial infarction and CVD mortality [1 study; 2621 people with severe psoriasis; moderate quality evidence][143]

In people with mild psoriasis there was a trend towards the risk compared with the general population or people without psoriasis being greater among those in younger age groups (i.e., decreasing risk attributable to psoriasis as age increased) for:

- Myocardial infarction [1 study; 127,139 people with mild psoriasis; very low quality evidence][124]
- Stroke [1 study; 34,371 people with mild psoriasis; moderate quality evidence][143]
- Ischaemic stroke [1 study; 36,765 people with mild psoriasis; moderate quality evidence][141]
- Composite of stroke, MI and CVD mortality [1 study; 34,371 people with mild psoriasis; moderate quality evidence][143]

In people with mild psoriasis there was no trend towards the risk compared with the general population being greater among those in younger age groups (i.e., decreasing risk attributable to psoriasis as age increased) for:

- CVD mortality [2 studies; 54,128 people with mild psoriasis; very low to moderate quality evidence][129,143]
- Myocardial infarction [1 study; 34,371 people with mild psoriasis; moderate quality evidence][143]
- Venous thromboembolism [1 study; 35,138 people with mild psoriasis; moderate quality evidence][142]
- Coronary revascularisation [1 study; 34,371 people with mild psoriasis; moderate quality evidence][143]

In people with psoriasis of varying severities there was a trend towards the risk compared with people without psoriasis being greater among those in younger age groups (i.e., decreasing risk attributable to psoriasis as age increased) for:

- Myocardial infarction [1 study; 36,702 people with psoriasis; very low quality evidence][120]
- Transient ischaemic attack [1 study; 36,702 people with psoriasis; very low quality evidence][120]

In people with psoriasis of varying severities there was no trend towards the risk compared with people without psoriasis being greater among those in younger age groups (i.e., decreasing risk attributable to psoriasis as age increased) for:

- Stroke [1 study; 36,702 people with psoriasis; very low quality evidence][120]

7.17.322 Treatments

Evidence summary

Two studies[144,145] provided data regarding the relative risk of cardiovascular disease in the people with psoriasis specifically treated with systemic therapy or phototherapy. One study[144] compared the incidence of acute myocardial infarction in the two treatment groups using data from a US medical and pharmacy claims database, while the other[145] compared the incidence of a composite outcome of cardiovascular events in each of the treatment groups with that in people with psoriasis not exposed to that intervention using data from medical care providers in Olmsted County, Minnesota, USA.

Table 40: Incidence of cardiovascular disease in people with psoriasis treated with systemic or phototherapy

Outcome	Study	Comparison	Multivariate adjusted risk estimate (95% CI)
CVD events	Maradit-Kremers 2012	Phototherapy vs no phototherapy	1.28 (0.55-2.98)
		Systemic therapy vs no systemic therapy	0.93 (0.49-1.75)
Acute MI	Abuabara 2011	Systemic therapy vs phototherapy	**Overall:** 1.10 (0.74-1.64) **Age 18-49:** 0.60 (0.28-1.30) **Age 50-70:** 1.37 (0.79-2.38)

HR: Hazard ratio
IRR: Incidence rate ratio
SMR: Standardised morbidity/mortality ratio

Evidence statements

In people with psoriasis:

- There was no statistically significant difference in the risk of acute MI between those treated with phototherapy and systemic therapy; however, there was a trend suggesting that systemic therapy may reduce the risk in younger people (age 18-49) but increase the risk in older people (age 50-70) [1 study; 25,554 people with psoriasis (4220 treated with systemics; 20,094 treated with phototherapy); very low quality evidence][144]
- There was no statistically significant difference in the composite outcome of the incidence of cardiovascular events (MI, revascularisation, cerebrocascular events, heart failure and cardiovascular death) between those treated and not treated with phototherapy or systemic therapy; however, there was a trend suggesting that systemic therapy may reduce the risk while phototherapy may increase the risk [1 study; 1905 people with psoriasis (191 treated with systemics; 178 treated with phototherapy); low quality evidence][145]

7.17.333 Summary

The data for the risk of cardiovascular disease in people with psoriasis mainly showed a statistically significant increase in cardiovascular disease compared with the general population or people without psoriasis; however, some results were discordant with this association. The results of Abuabara, Kaye, Gelfand, Lin, Mehta and Ahlehoff suggested that there is an increased risk for psoriasis patients compared to the general population or people without psoriasis, whereas the Wakkee and Brauchli studies showed no statistically significant differences. Of note, the latter two

studies controlled for fewer confounders (notably not diabetes) and were graded as very low quality for all outcomes, whereas considering only the moderate quality evidence gives consistent data to suggest a significantly higher risk in both mild and severe psoriasis for the key outcomes of stroke, MI and death from CVD, and in severe disease only for VTE. However, it was noted that the absolute increase in risk was low in the mild psoriasis group (see Appendix Q).

There were also two apparent trends demonstrating that:

- Risk is greater among those with more severe psoriasis
- With increasing age the risk attributable to psoriasis decreases

7.17.4 Cardiovascular disease risk factors

7.17.4.1 Incidence of cardiovascular disease risk factors in people with compared to people without psoriasis

Six cohort studies investigated the incidence of risk factors for cardiovascular disease.

One prospective study of female nurses[5] was conducted in the USA to investigate the risk of diabetes and hypertension. They utilised data from the Nurses Health Study II (NHSII) and compared those with a diagnosis of psoriasis to those without. The results were adjusted for age, smoking status, body mass index, alcohol intake and physical activity.

Another study also used data from NHSII, along with two other sources, the Nurses Health Study (NHS) and Health Professionals Follow-up Study (HPFS)[138] to investigate the risk of type 2 diabetes, comparing those with and without a diagnosis of psoriasis. The results were adjusted for age, smoking status, body mass index, race, family history of diabetes, hypertension, hypercholesterolemia, current aspirin use, multivitamin use, menopausal status, post-menopausal hormone use alcohol intake and physical activity. The diagnoses of psoriasis and diabetes were collected from patient self-report using validated questionnaires.

One population-based cohort study[116] investigated the risk of cause-specific mortality in patients with severe psoriasis using the GPRD. They included risk of mortality from liver disease, kidney disease and diabetes and adjusted for age and sex.

One cohort study[132] used the Hospital Discharge Register linked to the cause of death register in Finland between 1973 and 1995 to investigate the risk of mortality from smoking and alcohol. They standardised the ratios for age, sex and calendar period.

One cohort study[6] investigated the risk factors for myocardial infarction and other vascular diseases in patients with psoriasis compared to patients without psoriasis, using the GPRD. They included incidence of diabetes, hypertension, obesity, hyperlipidaemia, myocardial infarction, atherosclerosis, peripheral vascular disease and stroke and matched cohorts for age, sex and index date.

7.17.4.2 Evidence summary

Table 41: Incidence of cardiovascular disease risk factors in people with psoriasis compared with the general population or people without psoriasis

Outcome	Study	Multivariate adjusted risk estimate (95% CI)	
		All psoriasis patients	Severe psoriasis patients
Diabetes	QURESHI2009	IRR 1.63 (1.25-2.12)	-
	LI2011	IRR **Self-reported cases** NHS: 1.01 (0.83-1.22)	

	Study	Multivariate adjusted risk estimate (95% CI)	
		NHSII: 1.25 (1.05-1.49) HPFS: 0.91 (0.69-1.20) **Confirmed cases** NHS: 1.14 (0.92-1.42) NHSII: 1.46 (1.16-1.83)	
	BRAUCHLI2008	IRR 1.36 (1.20-1.53)	-
	KAYE2008	HR 1.33 (1.25-1.42)	-
Mortality from diabetes	ABUABARA2010	-	HR 2.86 (1.08-7.59)
	BOFFETTA2001		SMR 1.88 (1.20-2.79)
Hypertension	QURESHI2009	RR 1.17 (1.06-1.30)	-
	KAYE2008	HR 1.09 (1.05-1.14)	-
Hyperlipidaemia	KAYE2008	HR 1.17 (1.11-1.23)	-
Obesity	KAYE2008	HR 1.18 (1.14-1.23)	-
Mortality from alcohol and smoking – all categories	POIKOLAINAN1999[a]	-	SMR Men: 1.62 (1.52-1.71) Women: 1.54 (1.43-1.64)
Mortality from alcohol-related causes	BOFFETTA2001	-	SMR 6.37 (4.12-9.39)
Mortality from alcohol-related causes directly[(B)]	POIKOLAINAN1999[a]	-	Men: 4.46 (3.60-5.45) Women: 5.60 (2.98-8.65)
Mortality from alcohol-related causes indirectly	POIKOLAINAN1999[a]	-	SMR Men: 1.47 (1.20-1.75) Women: 1.31 (1.03-1.63)
Mortality from smoking-related causes	POIKOLAINAN1999[a]	-	SMR Men: 1.44 (1.33-1.56) Women: 1.61 (1.45-1.77)
Mortality from liver disease	ABUABARA2010	-	HR 2.03 (0.37-11.12)
	BOFFETTA2001	-	SMR 6.05 (4.49-7.97)
Mortality from kidney disease	ABUABARA2010	-	HR 4.37 (2.24-8.53)

(a) The study classified patients as moderate to severe. All patients were hospital inpatients.
(b) Includes underlying causes with direct reference to alcohol in the diagnosis i.e., alcohol-related psychosis, alchoholism, alcohol polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of the liver, unspecified alcoholic liver damage, alcoholic epilepsy, alcoholic pancreatitis, fetal alcohol syndrome, alcoholic withdrawal syndrome of the newborn, alcohol poisoning, and pregnancy, childbirth, or puerperium complicated by alcoholism.
HR: Hazard ratio
IRR: Incidence rate ratio
SMR: Standardised morbidity/mortality ratio

7.17.413 Evidence statements

The risk of diabetes was statistically significantly higher for those with psoriasis compared to an unexposed cohort [3 studies; 407,458 participants (78,570 with psoriasis); very low to moderate quality evidence][5,6,118].
However, in one study, the risk of diabetes varied between the cohorts, being statistically significantly higher for those with psoriasis compared to an unexposed cohort from the NHSII cohort, but not statistically significantly different for the NHS and HPFS cohorts [1 study; 184,395 participants (3074 people with psoriasis); moderate quality evidence][138]. The reason for this difference may have been that the NHSII cohort had a much younger mean age, which is likely to be the subset of the population where the most increased risk is found in those with psoriasis compared with people without psoriasis. The effect estimates showed a greater risk among those with psoriasis only including confirmed psoriasis cases rather than just those who self-reported a diagnosis of psoriasis [1 study; 184,395 participants (3074 people with psoriasis); moderate quality evidence][138].

The risk of mortality from diabetes was statistically significantly higher for those with psoriasis compared to an unexposed cohort [2 studies; 27,706 participants (13,376 people with psoriasis); very low quality evidence][116,117].

The risk of hypertension was statistically significantly higher for those with psoriasis compared to an unexposed cohort [2 studies; 342,009 participants (45,977 people with psoriasis); very low to moderate quality evidence][5,6].

The risk of hyperlipidaemia was statistically significantly higher for those with psoriasis compared to an unexposed cohort [1 study; 263,948 participants (44,164 people with psoriasis); very low quality evidence][6].

The risk of obesity was statistically significantly higher for those with psoriasis compared to an unexposed cohort [1 study; 263,948 participants (44,164 people with psoriasis); very low quality evidence][6].

The risk of mortality from alcohol and smoking was statistically significantly higher for those with moderate to severe psoriasis compared to an unexposed cohort [2 studies; 15,460 people with psoriasis; very low quality evidence] [117,132]

The risk of mortality from liver disease was not statistically significantly higher for those with severe psoriasis compared to an unexposed cohort [1 study; 17933 participants (3603 people with psoriasis); very low quality evidence][116]. However, the risk was statistically significantly higher in another study [1 study; 9773 people with psoriasis; very low quality evidence][117].

The risk of mortality from kidney disease was statistically significantly higher for those with severe psoriasis compared to an unexposed cohort [1 study; 17933 participants (3603 people with psoriasis); very low quality evidence][116].

7.17.414 Diabetes risk modification factors

In addition to stratifying for disease severity, one study gave information for different subgroups based on age.

7.17.415 Evidence summary

One study[118] provided data regarding the relative risk of diabetes in the psoriasis population compared with people without psoriasis for different age subgroups.

Table 42: Incidence of diabetes in people with psoriasis compared with people without psoriasis stratified by age

Outcome	Study	Multivariate adjusted risk estimate (95% CI)
		All psoriasis patients
Diabetes	BRAUCHLI2008	IRR **0-29 y:** 2.75 (1.24-6.13) **30-59 y:** 1.33 (1.09-1.61) **60-79 y:** 1.43 (1.21-1.69) **80+ y:** 1.12 (0.71-1.75)

IRR: Incidence rate ratio

7.17.4.6 Summary evidence statement

In people with psoriasis of **varying severities** there was a trend towards the risk compared with people without psoriasis being greater among those in the youngest age group (0-29 years) for:

- Diabetes [1 study; 65,449 participants (32,593 people with psoriasis); very low quality evidence][118]

7.17.487 Summary

The studies investigating risk factors for cardiovascular diseases suggest that people with psoriasis are at increased risk of developing cardiovascular risk factors (i.e., diabetes, hypertension, hyperlipidaemia and obesity) and death from cardiovascular risk factors compared to people without psoriasis, and this may be most pronounced among the youngest age group for diabetes. The highest quality evidence was for hypertension and diabetes.

7.17.5 Depression

One population-based cohort study used the GPRD to investigate the incidence of depression, in patients with psoriasis compared to an unexposed cohort without psoriasis. They adjusted for age and sex and reported results for all psoriasis patients, as well as subgroups for those with mild and severe disease.

7.17.591 Incidence of depression compared with people without psoriasis

Evidence summary

Table 43: Incidence of depression in people with psoriasis compared with people without psoriasis

Study	Multivariate adjusted risk estimate (95% CI)		
	All psoriasis	Mild psoriasis	Severe psoriasis
KURD2010	HR 1.39 (1.37-1.41), p=0.001	HR 1.38 (1.35-1.40), p=0.001	HR 1.72 (1.51-1.88), p=0.001

7.17.5.2 Evidence statements

The risk of depression was statistically significantly higher for those with psoriasis (mild and severe) compared to an unexposed cohort [1 study; 916,948 participants (149,998 with psoriasis); moderate quality evidence][3]

7.17.513 Risk modification factors for depression compared with people without psoriasis

Table 44: Incidence of depression in people with psoriasis compared with people without psoriasis stratified by age

Study	Multivariate adjusted risk estimate (95% CI)		
	All psoriasis	Mild psoriasis	Severe psoriasis
KURD2010	HR 20 y: 1.83 (1.78-1.87) 40 y: 1.46 1.44-1.49) 60 y: 1.17 (1.14-1.20)	HR 20 y: 1.81 (1.59-1.65) 40 y: 1.45 (1.42-1.47) 60 y: 1.16 (1.13-1.19)	HR 20 y: F: 2.51 (2.11-2.98) 20 y: M: 2.91 (2.39-3.54) 40 y: F: 1.85 (1.65-2.08) 40 y: M: 2.15 (1.84-2.51) 60 y: F: 1.37 (1.21-1.55) 60 y: M: 1.59 (1.34-1.88)

7.17.544 Evidence statements

The risk of depression was most greatly increased among the youngest age group of people with psoriasis compared with people without psoriasis [1 study; 916,948 participants (149,998 with psoriasis); moderate quality evidence][3].

7.1786 Cancer

7.17.691 Incidence of lymphoma compared with the general population or people without psoriasis

Eight studies[117,121-123,126,127,131] investigated the incidence of lymphoma among people with psoriasis compared with the general population or people without psoriasis. Note that two studies used the same population sample[121,131].

7.17.632 Evidence summary

Table 45: Incidence of lymphoma in people with psoriasis compared with the general population or people without psoriasis

Type of lymphoma	Study	Multivariate adjusted risk estimate (95% CI)		
		All psoriasis	Mild psoriasis	Severe psoriasis
All lymphoma	GELFAND2003	HR 2.94 (1.82-4.74)	-	-
	GELFAND2006	HR 1.35 (1.17-1.55), p<0.001	HR 1.34 (1.16-1.54), p<0.001	HR 1.59 (0.88-2.89), p=0.124
Non-Hodgkin's lymphoma	BOFFETTA2001	-	-	SIR 1.42 (0.89-2.15)
	FRENTZ1999[(a)]	SIR 1.4 (0.8-2.2)	-	-
	GELFAND2006	HR 1.14 (0.96-1.35), p=0.134	HR 1.15 (0.97-1.37), p=0.103	HR 0.73 (0.28-1.96), p=0.539
	HANNUKSELA-SVAHN2000	SIR 2.2 (1.4-3.4)		
	JI2009	SIR 1.31 (1.00-1.69)	-	-
	OLSEN1992[(a)]	HR 1.4 (0.7-2.7)	-	-
Hodgkin's lymphoma	BOFFETTA2001	-	-	SIR 0.36 (0.01-2.02)
	GELFAND2006	HR 1.48 (1.05-2.08), p=0.025	HR 1.42 (1.00-2.02), p=0.052	HR 3.18 (1.01-9.97), p=0.048
	HANNUKSELA-	SIR 3.3 (1.4-6.4)	-	-

Type of	Study	Multivariate adjusted risk estimate (95% CI)		
	SVAHN2000			
	OLSEN1992	HR 1.0 (0.1-4.9)	-	-
T-cell lymphoma	GELFAND2006	HR 4.34 (2.89-6.52), p<0.001	HR 4.10 (2.70-6.23), p<0.001	HR 10.75 (2.89-29.76), p<0.001

(a) Note that these two studies used the same population sample
HR: Hazard ratio
SIR: Standardised incidence ratio

7.17.643 Evidence statements

The incidence of lymphoma was statistically significantly higher for those with psoriasis compared to an unexposed cohort [2 studies; 102,7068 participants (154,915 people with psoriasis); low quality evidence][122,123]. However, one study showed that there was a statistically significant difference for those with mild psoriasis but not for those with severe psoriasis compared to an unexposed cohort, although the effect estimate indicated a higher risk (with more uncertainty) in the severe group [1 study; 919,147 participants; 153,197 people with psoriasis); low quality evidence][123].

There was no statistically significant increased risk for non-Hodgkin's lymphoma for people with psoriasis (mild and severe) compared to the unexposed cohort in 5 studies [185,738 people with psoriasis; very low to low quality evidence][117,121,123,127,131] but the incidence was statistically significantly higher in 1 other study [5687 people with psoriasis; very low quality evidence][126]

The risk of Hodgkin's lymphoma was statistically significantly higher for people with psoriasis compared to the unexposed cohort in 2 studies [158,884 people with psoriasis; low to very low quality evidence][123,126] but was not statistically significantly different in 2 studies [21,545 people with psoriasis; very low quality evidence][117,131].

The risk of T-cell lymphoma was statistically significantly higher for people with mild and severe psoriasis patients compared to an unexposed cohort [1 study; 153,197 people with psoriasis; low quality evidence][123]

7.17.654 Summary

The studies on the incidence of all lymphoma suggested that the risk of lymphoma is increased in psoriasis patients compared to the general population or people without psoriasis. Considering only the better quality evidence (graded as low rather than very low) suggests that Hodgkin's may have a significantly higher incidence among people with psoriasis, whereas non-Hodgkin's lymphoma may have a non-significantly higher incidence.

7.17.787 Incidence of skin cancer and renal tract cancers or overall cancer risk

Incidence of cancers of the skin or renal tract and overall cancer incidence was investigated in six studies[117,119,121,126,127,131]. Note that two of the studies were based on the same cohort but reported after different lengths of follow-up[121,131].

7.17.7.1 Evidence summary

Table 46: Incidence of cancers in people with psoriasis compared with the general population or people without psoriasis

Type of cancer	Study	Relative risk	p-value
Kidney	FRENTZ1999	SIR 1.2 (0.7-1.9)	-

Type of cancer	Study	Relative risk	p-value
	JI2009	SIR 1.50 (1.09-2.00)	-
	OLSEN1992	IRR 1.7 (1.0-2.8)	-
Kidney, renal pelvis	BOFFETTA2001	SIR 1.56 (1.04-2.25)	-
	HANNUKSELA-SVAHN2000	SIR 0.8 (0.4-1.4)	-
Bladder	FRENTZ1999	SIR 1.0 (0.7-1.4)	-
	JI2009	SIR 1.51 (1.20-1.88)	-
	OLSEN1992	IRR 1.0 (0.6-1.6)	-
Urinary bladder	CHEN2011	HR 3.18 (1.54-6.57)	
Bladder, ureter and urethra	HANNUKSELA-SVAHN2000	SIR 1.4 (0.9-2.1)	-
Bladder or kidney	BRAUCHLI2009	IRR 1.25 (0.84-1.85)	-
Melanoma	BRAUCHLI2009	IRR 0.83 (0.50-1.36)	-
	JI2009	SIR 0.95 (0.66-1.32)	-
	CHEN2011	HR 3.10 (1.24-7.71)	
	OLSEN1992	IRR 1.2 (0.5-2.4)	-
	HANNUKSELA-SVAHN2000	SIR 0.8 (0.3-1.6)	
SCC of the skin	BOFFETTA2001	SIR 2.46 (1.82-3.27)	
SCC of the skin	JI2009	SIR 2.08 (1.67-2.55)	-
Non-melanoma skin cancer	FRENTZ1999	SIR 2.46 (2.13-2.83)	p<0.05
	HANNUKSELA-SVAHN2000	SIR 3.2 (2.3-4.4)	
Other skin cancers	OLSEN1992	IRR 2.5 (2.0-3.0)	-
All cancers	BRAUCHLI2009	IRR 1.13 (1.02-1.24)	-
	PRIZMENT2011	HR 1.1 (0.9-1.4)	
	CHEN2011	1.66 (1.38-2.00)	

HR: Hazard ratio
IRR: Incidence rate ratio
SMR: Standardised morbidity/mortality ratio

7.17.742 Evidence statements

In people with psoriasis (observed risk of cancer) compared to an unexposed cohort (expected risk of cancer) the:

- Risk of kidney cancer was statistically significantly higher in the psoriasis group in 1 study [15,858 people with psoriasis; very low quality evidence][127] but was not statistically significantly different in 2 studies [6910 people with psoriasis; very low quality evidence][121,131].
- Risk of kidney and renal pelvis cancer was statistically significantly higher in 1 study [9773 people with psoriasis; very low quality evidence][117] but was not statistically significantly different in another study [5687 people with psoriasis; very low quality evidence][126].
- Risk of bladder cancer was not statistically significantly different in the psoriasis group in 2 studies [6910 people with psoriasis; very low quality evidence][121,131] but was statistically significantly higher in 2 studies [19,544 people with psoriasis; low to very low quality evidence][127,137].

- Risk of bladder, ureter and urethra cancer was not statistically significantly different in 1 study [5687 people with psoriasis; very low quality evidence][126].
- Risk of bladder or kidney cancer was not statistically significantly different in the psoriasis group in 1 study [32,593 people with psoriasis; very low quality evidence][119].
- Risk of SCC of the skin was statistically significantly higher in the psoriasis group in 2 studies [25,631 people with psoriasis; very low quality evidence][117,127].
- Risk of non-melanoma skin cancer was statistically significantly higher in the psoriasis group in 2 studies [12,597 people with psoriasis; very low quality evidence][121,126].
- Risk of melanoma cancer was not statistically significantly different in 4 studies [62,215 people with psoriasis; very low quality evidence][119,126,127,131] but was statistically significantly different in 1 study [3686 people with psoriasis; low quality evidence][137].
- Risk of all malignancies was statistically significantly higher in the psoriasis group in 2 studies [37,446 people with psoriasis; low to very low quality evidence][119,137], but not statistically significantly different in 1 study [719 people with psoriasis; low quality evidence][136].

7.17.8 Risk modification factors

A. Age subgroups

One study dichotomised the results into two age groups, less than 60 years and 60 years or more (see Table 47), while another study gave the relative risk for a range of age strata[137] (seeTable 48), both compared with people without psoriasis.

7.17.8.1 Evidence summary

Table 47: Incidence of various cancers in people with psoriasis compared with people without psoriasis with subgroups for age

Study	Cancer type	IRR (95% CI)	
		<60 years	≥60 years IRR (95% CI)
BRAUCHLI 2009	All cancer	1.19 (0.99-1.43)	1.13 (1.02-1.27)
	Lymphoma overall	2.38 (1.19-4.75)	1.59 (1.00-2.53)
	Lymphoma excluding CTCL	2.07 (1.00-4.28)	1.41 (0.87-2.28)
	Melanoma	0.83 (0.43-1.60)	0.84 (0.39-1.80)
	Bladder/kidney	0.78 (0.24-2.53)	1.37 (0.90-2.08)
	Metastasis	1.49 (0.50-4.42)	0.75 (0.48-1.17)

Table 48: Incidence of cancer in people with psoriasis compared with people without psoriasis with subgroups for age

Study	Cancer type	HR (95% CI)	p-value
CHEN2011	Any	**20-39 years:** 2.16 (1.15-4.05)	0.0162
		40-59 years: 1.84 (1.36-2.50)	<0.0001
		60-79 years: 1.50 (1.16-1.95)	0.0022
		>80 years: 0.91 (0.34-2.46)	0.8538

7.17.812 Evidence statements

In people with psoriasis (observed risk of cancer) compared to an unexposed cohort (expected risk of cancer) the incidence of the following cancers was greater among those aged <60 years compared with those aged ≥60 years [1 study; 73,404 participants (33,760 people with psoriasis); very low quality evidence][119]:

- All cancer
- Lymphoma overall and excluding CTCL
- Metastasis

In people with psoriasis (observed risk of cancer) compared to an unexposed cohort (expected risk of cancer) the risk of the following cancers was greater among those aged ≥60 years compared with those aged <60 years [1 study; 73,404 participants (33,760 people with psoriasis); very low quality evidence][119]:

- Melanoma
- Bladder/kidney

One study [203,686 participants (3686 with psoriasis); low quality evidence][137] also showed that there was a trend towards the relative risk in people with psoriasis being higher among those with younger onset of cancer.

188. Prior treatments

One study assessed the risk of any cancer in people with psoriasis depending on whether or not they had been exposed to PUVA, UVB or systemic therapies. They separately compared those with and without prior exposure with people without psoriasis (see Table 49), and also directly compared those with and without prior exposure to each other (see Table 50).

7.17.833 Evidence summary

Table 49: Incidence of cancer in people with psoriasis compared with people without psoriasis stratified by prior exposure to therapies

Study	Type of cancer	Relative risk	p-value
CHEN2011	Any	**PUVA**	
		Yes HR 2.03 (1.06-3.91)	0.033
		No HR 1.64 (1.35-1.99)	<0.0001
		UVB	
		Yes HR 1.01 (0.58-1.78)	0.98
		No HR 1.80 (1.48-2.19)	<0.0001
		Systemics	
		Yes HR 2.08 (1.40-3.12)	0.0003
		No HR 1.58 (1.28-1.94)	<0.000

Table 50: Incidence of cancer in people with psoriasis using PUVA and UVB compared to those not using these agents as the reference cohort

Study	Type of cancer	Relative risk	p-value
CHEN2011	Any	PUVA vs no PUVA 1.15 (0.58-2.28)	0.6906
		UVB vs no UVB 0.52 (0.29-0.95)	0.0324

Evidence statement

In people with psoriasis there was a non-statistically significant trend towards an increased risk of any cancer type among those with prior exposure to PUVA or systemic therapy. However, prior exposure to UVB statistically significantly reduced the risk of cancer [1 study [203,686 participants (3686 with psoriasis); low quality evidence][137].

C. Disease severity

Two studies addressed the relative risk of cancer in people with mild and severe psoriasis.

Both studies separately compared those with mild and severe disease with people without psoriasis (see Table 51), and one study also directly compared those mild and severe disease to each other (see Table 52).

7.17.824 Evidence summary

Table 51: Incidence of cancer in people with psoriasis compared with people without psoriasis stratified by disease severity

Study	Type of cancer	HR (95% CI)	
		Mild	Severe
PRIZMENT2011	Any	1.1 (0.9-1.4)	1.2 (0.8-1.8)
CHEN2011	Any	HR 1.59 (1.27-1.98)	HR 1.85 (1.33-2.57)

Table 52: Incidence of cancer in people severe with compared with mild psoriasis

Study	Type of cancer	Relative risk	p-value
CHEN2011	Any	Severe vs mild psoriasis 1.09 (0.74-1.63)	0.6583
PRIZMENT2011	Any	Trend across psoriasis severity as a continuous variable 0-no psoriasis; 1-mild; 2-severe	0.3

Evidence statements

- In people with psoriasis, there was no significant trend indicating that the risk compared with people without psoriasis was greater in severe disease for all cancers [1 study; 33,266 participants (719 with psoriasis); low quality evidence][136]
- In people with psoriasis, there was no significant difference in risk of all malignancies between those with mild versus severe disease, although there was a trend showing that the risk was greater in those with severe disease [1 study; 203,686 participants (3686 people with psoriasis); low quality evidence] [137].

7.17.855 Summary

The results for risk of renal tract cancer in people with psoriasis compared with people without psoriasis are very varied, with some conflicting data and poor quality evidence. The studies were mainly not adjusted for confounders except for matching on age and sex. Although, fewer studies demonstrated a statistically significantly high risk among people with psoriasis, these studies tended

to have larger sample sizes than those that did not show a significant increase, which may have been underpowered to detect the effect. Similarly, the larger studies reporting the risk of all cancers showed a statistically significantly high risk among people with psoriasis while one smaller study did not.

There was consistent evidence that the risk of non-melanoma skin cancer, but not melanoma skin cancer, is increased among people with psoriasis. All of the skin cancer studies used observed incidence in the psoriasis patients versus expected incidence in linked databases of the general population to calculate the relative risk.

Additionally, there was a trend towards the relative risk being greater for younger people with psoriasis. However, despite the apparent trends, there was no statistically significant increased risk among people with more severe psoriasis or with prior PUVA or systemic therapy exposure, although prior UVB exposure appeared to reduce the overall risk of malignancies.

7.17.9 Incidence of mortality from various cancers compared with people without psoriasis

Risk of cancer-related mortality was investigated in two studies[117,135]. One of the studies looked at people who were hospitalised for psoriasis[117].

7.17.9.1 Evidence summary

Table 53: Incidence of mortality from various cancers in people with psoriasis compared with people without psoriasis

Study	Type of cancer	Relative risk (HR)
Shu 2011	Kidney	1.58 (1.11-2.24)
	Urinary bladder	1.22 (0.84-1.76)
	Melanoma	1.85 (1.00-3.44)
	Skin SCC	3.16 (1.41-7.07)
	Non-Hodgkin's lymphoma	1.10 (0.79-1.54)
	All	1.26 (1.18-1.35)
Boffetta2001	Malignant neoplasm	1.30 (1.15-1.47)

Evidence statements

One study [1,013,503 participants (1746 with psoriasis); moderate quality evidence][135] demonstrated that in people with psoriasis (observed risk of cancer-related mortality) compared to an unexposed cohort (expected risk of cancer-related mortality), the incidence among those with psoriasis was statistically significantly greater for the following cancers:

- Kidney
- Melanoma
- Squamous cell carcinoma
- All

However, in the same study[135] there was no statistically significant difference in incidence of cancer-related mortality for the following cancers:

- Urinary bladder
- Non-Hodgkin's lymphoma

One study [9773 people with psoriasis; very low quality evidence][117] demonstrated that in people with psoriasis (observed risk of cancer-related mortality) compared to an unexposed cohort

(expected risk of cancer-related mortality), the incidence among those with psoriasis was statistically significantly greater for:

- Malignant neoplasms

7.17.10 Risk modification factors

One study provided evidence for the risk of cancer-related death in people with psoriasis compared with people without psoriasis stratified by disease severity and age.

A. Age subgroups

7.17.10.1 Evidence summary

Table 54: Incidence of mortality from various cancers in people with psoriasis compared with people without psoriasis stratified for age

Study	Type of cancer	Relative risk (HR)	
		Age ≤65 years	Age >65 years
SHU2011	Kidney	1.61 (0.97-2.68)	1.58 (0.97-2.58)
	Urinary bladder	0.63 (0.20-1.94)	1.39 (0.94-2.06)
	Melanoma	1.77 (0.79-3.94)	1.85 (0.69-4.94)
	Skin SCC	4.78 (1.52-15.02)	2.34 (0.75-7.30)
	Non-Hodgkin's lymphoma	1.44 (0.94-2.18)	0.79 (0.42-1.36)
	All	1.39 (1.28-1.52)	1.18 (1.08-1.29)

7.17.10.2 Evidence statements

One study [1,013,503 participants (1746 with psoriasis); moderate quality evidence][135] demonstrated that in people with psoriasis (observed risk of cancer-related mortality) compared to an unexposed cohort (expected risk of cancer-related mortality), the risk among those with psoriasis was greater for those in the younger age group for the following cancers:

- Kidney
- Squamous cell carcinoma
- Non-Hodgkin's lymphoma
- All

However, the risk among those with psoriasis was greater for those in the older age group for the following cancers:

- Urinary bladder
- Melanoma

B. Disease severity

7.17.10.3 Evidence summary

Table 55: Incidence of mortality from various cancers in people with psoriasis compared with people without psoriasis stratified for disease severity

Study	Type of cancer	Relative risk (HR)	
		Moderate-severe (one hospitalisation)	Severe (two or more hospitalisations)

Study	Type of cancer	Relative risk (HR)	
		Moderate-severe (one hospitalisation)	Severe (two or more hospitalisations)
SHU2011	Kidney	1.11 (0.67-1.84)	2.59 (1.59-4.22)
	Urinary bladder	0.92 (0.55-1.52)	1.90 (1.11-3.28)
	Melanoma	1.29 (0.54-3.11)	2.85 (1.19-6.82)
	Skin SCC	2.14 (0.53-8.56)	3.96 (1.48-10.61)
	Non-Hodgkin's lymphoma	0.93 (0.58-1.47)	1.32 (0.82-2.13)
	All	1.13 (1.03-1.23)	1.47 (1.33-1.63)

Evidence statements

One study [1,013,503 participants (1746 with psoriasis); moderate quality evidence][135] demonstrated that in people with psoriasis (observed risk of cancer-related mortality) compared to an unexposed cohort (expected risk of cancer-related mortality), the risk among those with psoriasis was greater for those with severe psoriasis for the following cancers:

- Kidney
- Urinary bladder
- Melanoma
- Squamous cell carcinoma
- Non-Hodgkin's lymphoma
- All

Summary

There was limited evidence for cancer-related mortality in people with psoriasis, however, there may be a higher cancer mortality rate among people with severe psoriasis compared with the general population.

All-cause mortality

Three retrospective cohort studies[117,134,143] investigated the risk of mortality in people with psoriasis for a variety of causes. People with mild and severe psoriasis were compared to the general population or people without psoriasis.

Incidence of all-cause mortality compared with the general population or people without psoriasis

Evidence summary

Table 56: Relative risk of mortality in psoriasis patients compared with the general population or people without psoriasis

Study	Hazard ratio/IRR (95% CI)		
	All patients with psoriasis	Mild psoriasis	Severe psoriasis
GELFAND2007	1.0 (0.99-1.04)	1.0 (0.97-1.02)	1.5 (1.3-1.7)
	Risk of mortality - Adjusted for risk factors for mortality*	-	1.42 (1.25-1.62)

Study	Hazard ratio/IRR (95% CI)		
	All patients with psoriasis	Mild psoriasis	Severe psoriasis
AHLEHOFF2011D	-	1.16 (1.11-1.20)	1.73 (1.54-1.94)
BOFFETTA2001	-	-	1.56 (1.48-1.64)

*Risk factors for mortality included smoking, BMI, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignant neoplasm, metastatic solid tumour, and AIDS.

Evidence statements

- In people with severe psoriasis the risk of all-cause mortality was statistically significantly higher compared to an unexposed cohort in 3 studies [4,762,982 participants (15,345 people with severe psoriasis); very low to moderate quality evidence][117,134,143]
- In people with mild psoriasis the risk of all-cause mortality was statistically significantly higher compared to an unexposed cohort in one study [4,040,257 participants (34,371 people with mild psoriasis); moderate quality evidence] [143], but not in another [712,952 participants (133,568 people with mild psoriasis); low quality evidence][134].

7.17.13 Risk modification factors

Two studies[134,143] investigated the risk of all-cause mortality in people with psoriasis stratified by age group.

7.17.13.1 Evidence summary

Table 57: Relative risk of mortality in psoriasis patients compared with the general population or people without psoriasis stratified by age

Study	Age subgroup	Hazard ratio/IRR (95% CI)	
		Mild psoriasis	Severe psoriasis
GELFAND 2007	35 years	-	2.5 (1.7-3.7)
	45 years	-	2.2 (1.6-1.9)
	55 years	-	1.9 (1.5-2.3)
	65 years	-	1.6 (1.4-1.9)
	75 years	-	1.4 (1.3-1.6)
	85 years	-	1.3 (1.0-1.5)
	95 years	-	1.1 (0.8-1.5)
AHLEHOFF2011D	18-50 years	1.26 (1.08-1.47)	2.87 (2.04-4.02)
	51-70 years	1.23 (1.15-1.31)	2.32 (1.96-2.74)
	>70 years	1.13 (1.08-1.19)	1.24 (1.05-1.48)

7.17.13.2 Summary evidence statement

In people with psoriasis the increased risk of all-cause mortality compared with the general population or people without psoriasis was greater among the younger age groups, and this trend was most apparent in the severe disease group [2 studies; 4,753,209 participants (173,511 people with psoriasis); low to moderate quality evidence][134,143]

Summary

The results suggested that there is a higher mortality rate among people with psoriasis compared with the general population or people without psoriasis, and the increased risk is most pronounced among younger individuals.

7.18 Economic evidence

No relevant economic evaluations were identified in the evidence search; however, given the nature of the clinical question being asked, formal economic evaluation would neither be appropriate nor informative. Instead, one study by Kimall and colleagues[146] was included that compared the health care resource use and direct medical cost of treating comorbidities in addition to treating psoriasis with treating psoriasis alone. This study is summarised in the narrative below.

Another cost of illness study by Crown and colleagues[147] was excluded. This study aimed to compare the annual direct medical expenditure of patients with psoriasis treated with systemic/phototherapy compared to a matched sample without psoriasis. Although they showed that the psoriasis cohort was more likely to have certain comorbidities than the non-psoriasis cohort, the estimates of health care use and direct medical costs were not broken down in such a way as to be informative[m].

Kimball and colleagues extracted data from the Ingenix Impact National Managed Care Database (IMPACT)[n] for patients with at least one diagnosis of psoriasis and who were at least 18 years old. They randomly selected from all the dates of health services coded with a diagnosis of psoriasis in the database and then defined the study period for each patient as the 6-month period after the index date. Patients were assigned then to one of two cohorts:

Cohort 1: Patients with psoriasis and a diagnosis of one or more of the following comorbidities in the 6-month study period:

- Psoriatic arthritis
- Cardiovascular disease
- Depression
- Diabetes
- Hyperlipidemia
- Hypertension
- Obesity
- Cerebrovascular disease
- Peripheral vascular disease

Cohort 2: Patients with psoriasis but without a diagnosis of any of these comorbidities in the 6-month study period

In addition to comparing the cohort with comorbidities to the cohort without, a subgroup analysis was performed for each comorbidity.

Table 58: Characteristics of sample patient population

Characteristics	Patients with comorbidity	Patients without comorbidity
Patients	58,320 (50.9%)	56,192 (49.1%)
Age, years (mean±SD)	52.1 ± 12.9	40.5 ± 12.4
Sex (% male)	51.4%	47.9%
Psoriasis severity[a]		

m The authors showed that 1) total expenditure was higher for patients with psoriasis receiving systemic/phototherapy than patients without psoriasis; 2) total expenditure among was higher for patients with psoriasis and comorbidities than among patients without psoriasis and the same comorbidities.

n IMPACT is an administrative insurance claims database that contains medical and pharmacy service data of more than 60 million covered people in 46 health insurance plans from all census regions of the USA. It includes information on inpatient stay, medical services use and pharmacy claims for prescription drugs.

Characteristics	Patients with comorbidity	Patients without comorbidity
Mild	85.4%	89.4%
Moderate to severe	14.6%	10.6%

(a) Because the claims database does not record any clinical assessment data for severity, treatments received during study period were used as a proxy for severity. Patients who received at least one topical therapy or no psoriasis medication at all were considered to have mild psoriasis. Patients who were prescribed systemic therapy (phototherapy, methotrexate, ciclosporin or acitretin) were considered to have moderate to severe psoriasis.

7.18.151 Health care resource use

Health care resource use during the study period was compared between the two cohorts. Adjusted incidence rate ratios (IRRs) and odds ratios (ORs) between the cohorts were calculated with their respective 95% confidence intervals (Table 59). The IRR reflects the difference between groups in resource utilisation during the 6-month period. ORs demonstrate the relative likelihood of having at least one inpatient admission or emergency department visit during the study period. Ratios were adjusted using multivariate regression models, controlling for age, sex and psoriasis severity.

Table 59: Adjusted IRRs and Ors of health care resource utilisation

Comorbidity	Inpatient		Outpatient	Emergency department	
	IRR	OR	IRR	IRR	OR
Any comorbidity	**2.27 (2.13 to 2.42)**	**2.21 (2.08 to 2.36)**	**1.53 (1.52 to 1.55)**	**1.71 (1.63 to 1.79)**	**1.58 (1.51 to 1.65)**
Psoriatic arthritis	1.31 (1.17 to 1.47)	1.38 (1.24 to 1.53)	1.08 (1.05 to 1.10)	1.10 (0.99 to 1.21)	1.05 (0.96 to 1.16)
Cardiovascular disease	4.19 (3.90 to 4.50)	4.33 (4.06 to 4.62)	1.47 (1.45 to 1.50)	2.28 (2.13 to 2.45)	2.06 (1.93 to 2.20)
Depression	2.33 (2.15 to 2.52)	2.07 (1.93 to 2.23)	1.82 (1.79 to 1.85)	2.11 (1.99 to 2.25)	1.89 (1.79 to 2.01)
Diabetes	2.06 (1.90 to 2.22)	1.92 (1.80 to 2.06)	1.39 (1.37 to 1.42)	1.82 (1.70 to 1.95)	1.62 (1.51 to 1.73)
Hyperlipidemia	1.08 (1.02 to 1.15)	1.15 (1.09 to 1.22)	1.25 (1.23 to 1.26)	1.15 (1.09 to 1.21)	1.16 (1.10 to 1.22)
Hypertension	1.84 (1.73 to 1.95)	1.86 (1.76 to 1.97)	1.28 (1.26 to 1.30)	1.66 (1.57 to 1.74)	1.53 (1.45 to 1.60)
Obesity	2.25 (2.00 to 2.52)	2.24 (2.03 to 2.47)	1.34 (1.30 to 1.37)	1.63 (1.48 to 1.80)	1.63 (1.49 to 1.79)
Cerebrovascular disease	3.74 (3.35 to 4.16)	3.70 (3.39 to 4.03)	1.54 (1.50 to 1.59)	2.74 (2.48 to 3.03)	2.53 (2.30 to 2.78)
Peripheral vascular disease	3.22 (2.87 to 3.62)	3.11 (2.83 to 3.42)	1.53 (1.49 to 1.58)	2.42 (2.17 to 2.70)	2.16 (1.95 to 2.39)

(a) IRR, Incidence rate ratio: reflects the difference between groups in resource utilisation incurred during the 6-month study period
(b) OR, odds ratio: demonstrate the relative likelihood of having at least one inpatient admission or emergency department visit during the 6-month study period

Patients with psoriasis and comorbidities used more health care resources than did patients with psoriasis without comorbidities. Patients with comorbidities had 2.27 times as many hospitalisations, 1.53 times as many outpatient visits and 1.71 times as many emergency department visits as patients without comorbidities. Patients with psoriasis with comorbidities had a greater likelihood of being hospitalised or visiting the emergency department, with odds ratios of 2.21 and 1.58 respectively.

Overall, patients with psoriasis with any of the identified comorbidities were more likely to use health care resources and used medical services more often during the 6-month study period than patients with psoriasis with no comorbidities.

7.18.142 Health care costs

Costs were measured in 2007 US dollars and included costs associated with pharmacy, inpatient, emergency department, outpatient and other medical services. Table 60 presents the differences in total costs incurred during the 6-month study period between the two cohorts (comorbidity cohort compared to non-comorbidity cohort).

Table 60: Incremental costs associated with patients with comorbidities

Comorbidity	Adjusted cost difference	95% Confidence interval
Any comorbidity	**1408**	**699 to 2118**
Psoriatic arthritis	1071	531 to 1610
Cardiovascular disease	3405	1690 to 5121
Depression	1882	934 to 2830
Diabetes	1821	904 to 2738
Hyperlipidemia	53	26 to 79
Hypertension	1210	600 to 1819
Obesity	1645	816 to 2474
Cerebrovascular disease	3993	1981 to 6004
Peripheral vascular disease	3470	1722 to 5219

Costs were adjusted using multivariate regression models controlling for age, sex and psoriasis severity. Converted from US$ (1£=0.645US$) using 2007 purchasing power parities[35]

7.18.22 Economic considerations

The evidence from this study confirms largely what we already suspected to be true. That is, patients with psoriasis and significant comorbidities use health care services with greater frequency and in greater quantity than patients with psoriasis alone. The impact of comorbidities on direct health care costs may be attributable to additional resources consumed for treating these comorbid illnesses. In addition, the coexistence of psoriasis and another illness may exacerbate the adverse effects of each condition. Indeed, the presence of comorbidities in patients with psoriasis may complicate the management of both diseases. Some of these chronic comorbidities require long-term treatment, and some of these treatments may exacerbate psoriasis itself or may cause potential drug-drug interactions and interfere with psoriasis therapies.

There are some limitations of this evidence that are worth noting:

- This is a study based on an insurance claims database from the United States.
- Insurance claims database does not provide clinical assessment data of psoriasis. The treatment information was used as a proxy for disease severity, which although reasonable, is not perfect.
- It is possible that claims data may not contain all comorbidities present in the patients. This is because diagnostic codes are used for reimbursement purposes and a comorbid condition is entered into the database only when a patient receives care specifically for that condition. It is

possible that comorbidities that were not severe enough to require health care services or medication use were not coded; thus comorbidities may be underestimated.

- Although the authors controlled for age, sex and psoriasis severity in the regression analysis, the estimated incremental cost associated with a particular comorbidity cannot be interpreted as entirely attributable to the comorbidity alone. There may be other confounders, not controlled for, that may have contributed to increased costs. Therefore, the treatment costs of a particular comorbidity were estimated as the additional cost for treating a typical patient with psoriasis with the comorbidity compared with a similar patient with psoriasis who did not have the comorbidity.

7.18.3 Evidence statements

- One economic burden study showed that patients with psoriasis with comorbidities such as cardiovascular disease, depression, diabetes, obesity and hypertension are likely to incur greater health care costs, driven predominantly by increased utilisation of medical services, than those without comorbidities.

7.19 Recommendations and link to evidence

Recommendations on identification of comorbidities	**21. Offer a cardiovascular risk assessment using a validated risk estimation tool to adults with severe psoriasis at presentation, and offer further assessments every 5 years, or more frequently if indicated following risk assessment. For further information see 'Lipid modification' (NICE clinical guideline 67).** **22. Discuss risk factors for comorbidities with people who have psoriasis of all severities. Explain that they are at higher risk of hypertension, diabetes, obesity and hyperlipidaemia than people without psoriasis. Offer preventative advice and healthy lifestyle information in line with the following NICE guidance:** • **'Lipid modification' (NICE clinical guideline 67)** • **'Obesity' (NICE clinical guideline 43)** • **'Preventing type 2 diabetes: population and community-level interventions in high-risk groups and the general population' (NICE public health guidance 35)** • **'Prevention of cardiovascular disease at population level' (NICE public health guidance 25)** • **'Alcohol-use disorders: preventing the development of hazardous and harmful drinking' (NICE public health guidance 24)** • **'Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities' (NICE public health guidance 10).** **23. For people with multiple comorbidities and any type of psoriasis needing second- or third-line therapy ensure multidisciplinary working and communication between specialties and, if needed, interdisciplinary team working (for**

	example when both skin and joints are significantly affected)[o]. **24. Be aware that psoriasis is a risk factor for venous thromboembolism, especially in people with severe psoriasis and:** • **explain this risk to people with psoriasis** • **offer advice on how to minimise the risk (for example, during hospital admission, surgery or periods of immobility)** • **manage the risk in line with 'Venous thromboembolism: reducing the risk' (NICE clinical guideline 92).**
Future research recommendations	**8. Does treating psoriasis modify the risk of cardiovascular disease and are there any clinical (for example, demographic, phenotypic) or laboratory (for example genetic or immune markers) that identify those most likely to benefit?** **9. Does reduction of relevant, modifiable cardiovascular risk factors (for example weight loss, exercise or statins) improve psoriasis and are there particular demographic , phenotypic or other biomarkers (for example age or disease severity) that identify those most likely to benefit?** **10. What is the natural history of psoriasis and are there any adverse prognostic markers that identify individuals at risk of severe recalcitrant disease who might benefit from early intervention?**
Relative values of different outcomes	Outcomes: • Incidence of comorbidities • Death Comorbidities: • Obesity • Cardiovascular disease (including stroke) • Alcohol-related disease • Cancer (skin cancer, lymphoma, all cancer) • Liver disease • Diabetes mellitus • Hypertension • Depression • Inflammatory bowel disease Some studies reported composite outcomes, which are considered to be less reliable as they often include outcomes that are quite different e.g. lipid levels are not as associated with stroke as with MI. Also, revascularisation is difficult to interpret in an undefined population as the reason for revascularisation is unclear. The specific types of cancer were chosen as those with a clinical

o For further information see 'The National Service Framework for long-term conditions'

	reason for expecting the incidence to be higher among people with psoriasis. Skin cancer was assessed based on the known risk associated with phototherapy and the tendency of people with psoriasis to seek out sun to improve their condition; lymphoma was assessed based on the knowledge of high profile studies reporting an association and literature on immunosuppressants causing lymphoma); bladder/renal tract cancers are a concern because tar-based products have been indicated as carcinogenic). Finally, all cancer as a composite outcome was included to address the concern over the impact of long term immunosuppression caused by some systemic treatments for psoriasis and the reportedly high prevalence of smoking and alcohol use.
Trade off between clinical benefits and harms	Overall, focussing on the higher quality evidence that used appropriate regression analysis accounting for time and key confounders and considering both the absolute and relative risks, there was consistent data to suggest a significantly higher risk in severe psoriasis for the key outcomes of stroke, MI and death from CVD. The GDG noted that the absolute increase in incidence in the mild psoriasis group and in young people with psoriasis was unlikely to represent a clinically relevant elevation of risk. The GDG also discussed the evidence that patients with severe psoriasis are at a clinically relevant risk for venous thromboembolism and pulmonary embolism and therefore should be offered advice on how to minimise risk. This was considered particularly important because inflammatory disease is a recognised risk factor for venous thromboembolism risk for inpatients (ref CG92) and people with severe psoriasis may also be relatively immobile at times, for example due to hospital admission/daycare treatment with dithranol. There was also reliable evidence indicating that people with psoriasis are at increased risk of developing diabetes and hypertension, and that this risk may be most pronounced among the youngest age group for diabetes. The risk of depression was clinically significantly higher for those with psoriasis (mild and severe) and was most greatly increased among the youngest age group of people with psoriasis. The GDG did not wish to stigmatise people with psoriasis but felt that by emphasising the need to routinely question about alcohol intake, this would reduce stigmatisation.
Economic considerations	The evidence from Kimball and colleagues[146] confirms largely what the GDG already suspected to be true. That is, patients with psoriasis and significant comorbidities use health care services with greater frequency and in greater quantity than patients with psoriasis alone. The impact of comorbidities on direct health care costs may be attributable to additional resources consumed for treating these comorbid illnesses. In addition, the coexistence of psoriasis and another illness may exacerbate the adverse effects of each condition. Indeed, the presence of comorbidities in patients with psoriasis may complicate the management of both diseases. Some of these chronic comorbidities require long-term

	treatment, and some of these treatments may exacerbate psoriasis itself or may cause potential drug-drug interactions and interfere with psoriasis therapies. The GDG considered limitations of the evidence, such as its source (i.e. US insurance claims database), how it identified and categorised patients (i.e. using treatment information as a proxy for disease severity) and whether it may have under or overestimated comorbidities. In particular they considered that the estimated incremental cost associated with a particular comorbidity could not be interpreted as entirely attributable to the comorbidity alone. There may be other confounders, not controlled for, that may have contributed to increased costs. Therefore, the treatment costs of a particular comorbidity were estimated as the additional cost for treating a typical patient with psoriasis with the comorbidity compared with a similar patient with psoriasis who did not have the comorbidity. The GDG considered that early and proactive identification of possible comorbidities, including depression, diabetes and/or cardiovascular conditions, was likely to represent good value for NHS resources. It is unlikely that these additionally assessments and/or provision of advice will incur any extra costs to the NHS as these patients may receive such services as part of their regular consultations with GPs and/or dermatologists. The GDG considered that early identification and intervention, where appropriate, could improve patients' quality of life in the short and longer term at a modest additional cost.
Quality of evidence	Many of the studies used a short duration of follow up (less than 10 years), which may be too short to detect some comorbidities. Not all studies had carried out the ideal analysis using multivariable regression and there was also variation in the number of confounders that were adjusted for. Cancer studies were less well controlled than cardiovascular studies, but all studies had at least one key confounding variable that had not been adjusted for in the analysis. The studies varied in terms of the statistics reported; some studies reported hazard ratio instead of relative risk. Most evidence was from retrospective studies, which are associated with a risk of bias (misclassification of diseases / severity). The General Practice Research Database (GPRD) data was collected prospectively and analysed retrospectively in the studies. It was unclear from the papers if participants who were lost to follow up were included, but the GDG felt it likely that only those with full data were included. The following studies were at a particularly high risk of bias owing to the exposed group (people with psoriasis) and unexposed group (people without psoriasis) being sampled from different cohorts (which creates a considerable extra confounding factor): • BOFFETTA 2001

- FRENTZ 1999
- HANNUKSELA- SVHAN 2000
- MALLBRIS 2004
- OLSEN 1992
- POIKOLAINAN 1999

The Brauchli study controlled for few confounders; but excluded people with prior cardiovascular diagnosis, which may be the most significant risk factor for further cardiovascular events, whereas Gelfand and Kaye did not.
The Lin study excluded people with previous diagnosis of acute myocardial infarction. The study population was Taiwanese and included those accessing ambulatory care. In the UK setting, this would translate as people with moderate to severe disease.
Brauchli and Gelfand used the same data source (GP databases from the UK).
The Gelfand study categorised participants as severe if they had previously received treatment with systemic drugs.
Approximately 17% of participants in this group had received azathioprine, but this is not routinely used for psoriasis in clinical practice.
Possible reasons for the differences in findings for the incidence of stroke between the UK GPRD studies, apart from the differences in controlling for confounders:

- Gelfand included all patients with a psoriasis diagnosis (prevalent or incident), not excluding those with a history of MI, whereas Brauchli only included incident psoriasis and incident MI (excluded cases diagnosed with MI prior to first psoriasis diagnosis). This is an advantage of the Brauchli study, which would allow more inference about the causal role of psoriasis; however, it would also have resulted in more patients with early psoriasis being included, which may result in a less severe cohort, and given the evidence that the association is stronger in those with more severe disease, this may explain why no association was seen in the Brauchli study, while it was in the Gelfand study (particularly in the severe subgroup)
- The comparison group in the Gelfand study was much larger (five controls per person in the psoriasis group) whereas in the Brauchli study, there was one control per person with psoriasis; and the psoriasis group was also much larger in the Gelfand study; therefore this study would have had greater power to detect a difference.

The Wakkee study only included people who had been hospitalised for psoriasis or psoriatic arthritis, and who had also received efalizumab / fumarates. It excluded people who had received ciclosporin, methotrexate, or TNF antagonists. The GDG understood the rationale behind this (i.e. ensuring appropriate people included, as efalizumab and fumarates are only ever given for psoriasis). However there was concern that this approach would exclude the majority of people with psoriasis, resulting in a

	population that is not representative. Therefore the GDG had reservations about the population of this study. Some of the studies that did find an association between psoriasis and CVD risk had performed multiple sensitivity analyses that demonstrated that the results were robust to a number of changes in the analyses/assumptions. Importantly, in one study (Ahelhof2011E) for the outcome of ischemic stroke this included demonstrating that the estimated magnitude of any unmeasured confounder, assuming it had a prevalence of 20%, that could nullify the results would have to be greater than the effects and distribution of any of the measured confounders (e.g. valvular heart disease or prior myocardial infarction). This supports the suggestion that psoriasis is an independent risk factor for cardiovascular disease. Ahelehof also found that results were not different if the diagnostic criteria for psoriasis were less restrictive (first vitamin D analogue prescription or first diagnosis); neither did exclusion of all patients with in- or out-patient hospital contacts up to 1 year prior to study start significantly alter the results. The results were also similar when using a control cohort matched for age and gender from the full population; specifically for stroke, exclusion of all patients with prior MI or censoring of patients at the time of surgical procedure, valvular heart disease or anti-thyroid treatment did not significantly alter the results. Similarly, Mehta 2010 and 2011 demonstrated that the association between psoriasis and MACE/cardiovascular death held in a number of scenarios, including the exclusion of certain treatments: • Inclusion of patients with at least 1 GP visit per year on average • Exclusion of methotrexate • Exclusion of oral retinoids or ciclosporin • Restricting to patients who received oral retinoids • Exclusion of psoriatic arthritis • BMI included as a covariable • Again, in Glefand 2006A, the following sensitivity analyses did not alter the results: only patients with at least 6 months of follow-up time and could not have had an MI in the first 6 months to ensure the capture of incident, not prevalent, MIs. • Restricting the population to only include patients observed at least once per year by the general practitioners. • Including only those with BMI data available and adjusting for this variable Similarly, in Gelfand 2009, the following sensitivity analyses did not alter the results: • Only patients with at least 6 months of follow-up time and could not have had an MI in the first 6 months to ensure the capture of incident, not prevalent, MIs. • Restricting the population to only include patients observed at least once per year by the general practitioners.

	• Including adjustment for BMI, or atrial fibrillation • Exclusion of methotrexate • Exclusion of oral retinoids or ciclosporin • Restricting to patients who received oral retinoids • Exclusion of psoriatic arthritis The Qureshi study was prospective and the only one reporting the outcome of diabetes to exclude those with known diabetes prior to psoriasis diagnosis. The GDG discussed potential limitations with the data, and how robust a method logistical regression is for adjusting for confounders. There is the possibility of residual confounding and also there may be unknown interactions between residual confounders. Also participants only receive a code for a comorbidity if they have been treated for it, so participants may have a comorbidity that hasn't been coded because it hasn't been treated. Therefore, databases do not capture all comorbidities. The studies looking at the risk of cancer were considered to be too poorly controlled for confounders to be used as a basis for a recommendation. The apparent increase in risk of lung and pancreatic cancer were considered to be potentially linked to a higher prevalence of smoking and drinking among people with psoriasis. There was insufficient data for any of the outcomes regarding the impact of different treatments for psoriasis on the incidence of comorbidities
Other considerations	Primary prevention and management strategies are the same for all types of cardiovascular disease; therefore the GDG felt it appropriate to consider all cardiovascular diseases together. From the evidence we do not know if there is an unknown component to the increased risk of cardiovascular disease, e.g. people with psoriasis take less exercise, but across all of the cardiovascular disease outcomes from the highest quality studies there was generally consistent evidence that risk is increased in people with psoriasis, particularly if the psoriasis is severe. The GDG noted that whilst the evidence indicated an association between psoriasis and CVD, and the risk factors for CVD, there were a number of outstanding uncertainties that are of importance to patients: whether treating CVD risk factors might improve psoriasis; whether treating psoriasis reduces CVD and whether it is psoriasis per se, or certain lifestyle choices as a result of psoriasis that drives increased risk of CVD. The GDG were mindful that psoriasis is a common disease and in the majority of people (who do not have severe disease) the absolute risk of CVD is low so recommending formal CVD assessment for all patients may cause undue anxiety for an important majority. The GDG agreed that the size of risk for people with severe disease justified making a recommendation for formal CVD assessment in all patients with severe disease (as defined in the introduction).

	There was debate about when and how often to assess. Current guidance on screening for CVD in the general population if the 10 year CVD risk is less than 20% is to review every 5 years, and if it is greater than or equal to 20% yearly recall is suggested. The GDG took into account that patients with psoriasis would probably already require review for topical treatment efficacy and assessment for the presence of psoriatic arthritis on an annual basis. Given that it is likely that they would already be under follow up in specialist units, the GDG agreed that at least every 5 years would be warranted or more frequently if indicated by the CVD assessment. The GDG acknowledged the potential to create additional work for primary care. Assessment for cardiovascular disease in specialist / dermatology care is not routine and current practice in dermatology is thought to be variable, therefore a recommendation about assessment for cardiovascular disease would apply to secondary and primary care. The GDG considered that the evidence for the increased incidence of traditional risk factors for cardiovascular disease (smoking, alcohol related morbidity and mortality, obesity, hypertension, hyperlipidaemia and diabetes) along with the data showing the increased risk of cardiovascular disease outcomes indicated the need to ensure people with psoriasis were given appropriate information and support to make relevant lifestyle changes. Although the evidence was only robust for diabetes out of all of the risk factors assessed, it was felt reasonable to recommend information to be given in relation to all cardiovascular disease risk factors in light of the co-dependency among them as well as the clear increase in cardiovascular events, which suggests that raising awareness would be of benefit to modify the known risk factors. The evidence on depression, and GDG experience, indicated the need to always consider depression when assessing patients with psoriasis. The evidence for lymphoma is equivocal and therefore the GDG did not wish to make any recommendations about lymphoma.

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8 Topical therapy

Topical therapy in some form or another is prescribed to virtually everyone with psoriasis presenting for treatment. The majority of people with psoriasis have localised disease and here, topical therapy is the principal approach to treatment. In more extensive and severe forms of psoriasis, topical therapy remains an important adjunct to second and third line therapy and remains the mainstay of treatment in people who do not want or cannot use second or third line therapies.

Corticosteroids, vitamin D3 and its analogues, calcineurin inhibitors, retinoids, tar, dithranol and keratolytic agents such as salicylic acid and urea are available for topical use for psoriasis and come in a vast array of different formulations, combinations, potencies and dilutions. Some of the topical agents in common use - particularly in specialist settings - are 'special manufacture' medicines ('Specials')[148] -. Preparations such as dithranol in Lassar's paste and crude coal tar are sometimes referred to as 'complex topicals' as they usually needs to be administered in specialist settings by trained individuals to optimise outcomes and minimise adverse effects including burning and staining of skin.

For most patients, topical treatments are prescribed for home use to self-manage psoriasis. Variable outcomes are reported with the use of topical therapies and much of this variation is likely to relate to problems with adherence. Adherence, previously referred to as compliance, is the degree to which a patients' behaviour taking or using treatments corresponds with recommendations from a healthcare professional. Adherence can be sub-divided into primary adherence, which is redemption of prescriptions and secondary adherence, which relates to correct use of treatments. Primary adherence in one study was found to be low with 30% of patients not collecting their prescriptions[38]. This study also revealed that 95% of patients under-dosed with their topical treatment. Moreover, secondary adherence to topical therapies is variable with one study showing that 39% of patients did not adhere to the recommended treatment regime[149] while another reported a mean adherence of 72%[150]. There are several factors that influence secondary adherence such as the cosmetic acceptability of the product, time required for application, dosage regimes as well as ease of use. The cosmetic acceptability of a product is related to the formulation and can have an impact on secondary adherence. In one survey of psoriasis patients prescribed topical therapies it was found that the greasiness of the preparation was responsible for non-adherence in 11% of patients[151]. Ointments have been traditionally used due to perceived superior efficacy and the fact that the vehicle is more effective at hydrating dry, scaling psoriatic skin. However, some evidence suggests that patients prefer a cream or gel formulation[152] and potential differences in vehicles may have a negative impact on adherence and should be discussed with patients when prescribing topical agents.

Although several factors influence adherence, one suggested technique to improve adherence is through patient education. In a recent focus group study with psoriatic patients, it was noted how patients identified that instruction on the correct use topical treatments was essential but often absent from consultations. The study also revealed the erratic and inconsistent use of topical treatments by patients, therefore highlighting the need for more effective community-based support[153]. There is some evidence that adjunctive patient education improves both quality of life and reduces disease severity in patients with skin disease[154] and this approach has been successfully deployed in studies with psoriatic patients[155,156].

Health professional prescribing topical therapies should have sufficient product knowledge including the effect of the treatment on psoriatic plaques and any adverse effects on the surrounding skin. Prescribers also need to engage with patients in an attempt to ascertain the psychological impact of their psoriasis and to agree therapeutic goals in an effort to improve adherence. Support for patients with dexterity or disability problems can be provided together with advice to patients to support adherence. In addition, the medicines use review service may provide information about usage of

treatments and where necessary, provide knowledge to help to resolve poor or ineffective use of therapies.

The wide array of potential topical agents available requires that healthcare professionals treating psoriasis deploy a therapeutic strategy that is based on the best available evidence. Such an approach is justified, not only to endeavour to provide a high standard of care but to ensure that referrals to specialist centres are appropriately managed. In an effort to provide health professionals with an algorithm for sequencing of topical agents and for criteria that would trigger a referral, we examined the evidence to determine the most suitable strategic approach for the individual patient.

There is a general consensus amongst clinicians and patients that emollients are useful adjunctive therapy in the management of inflammatory skin disease including psoriasis. Emollients help to restore pliability to the skin and can improve the cosmetic appearance of plaques by reducing shedding of scale. Emollients also appear to reduce pruritus and can help to reduce cracking of the skin which can be extremely painful. The GDG felt that the use of emollients in psoriasis was widespread and of accepted value, and review of the evidence was unlikely to yield important data that would justify recommending a change in practice. We have therefore limited our evidence review to active topical therapies in psoriasis. We have also focussed our review on plaque psoriasis only for pragmatic reasons, given the number of studies in this area, but acknowledge that topical therapies are also key components of treatment for other types of psoriasis.

The face, flexures (including genitals) and scalp are often described as 'difficult to treat' since the face and flexures are especially vulnerable to tolerability and toxicity issues, and the scalp is difficult to access and often resistant to treatment. These sites are also often 'high impact' sites, and in one recent patient survey[28] the number of people with scalp psoriasis was notable (1158 out of 1618 respondents reported having scalp psoriasis) and clearance of visible areas was rated as important. The GDG therefore felt these sites should be given special consideration when considering the evidence. The GDG were also interested to establish the timelines for treatment response of the various agents to guide clinicians on when to review patients in order to optimise outcomes, and limit use of ineffective agents. The GDG posed the following questions:

In people with chronic plaque psoriasis, (i) what are the clinical effectiveness, safety, tolerability, and cost effectiveness of topical vitamin D and vitamin D analogues, potent or very potent corticosteroids, tar dithranol, and retinoids?; and (ii) at what time interval should the patient be reviewed to assess the effectiveness of treatment with topical therapy?

In people with psoriasis at difficult-to-treat sites (scalp, flexures including genitals, face), (i) what are the clinical effectiveness, safety, tolerability and cost-effectiveness of available topical therapies; and (ii) at what time interval should the patient be reviewed to assess the effectiveness of treatment with topical therapy?

8.1 Topical therapies for trunk and limb psoriasis

8.1.1 Methodological introduction

A literature search was conducted for RCTs or systematic reviews that addressed the efficacy and safety of topical vitamin D and vitamin D analogues, potent or very potent corticosteroids, combined vitamin D or vitamin D analogue and potent corticosteroid, concurrent vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening) tar, dithranol and retinoids for induction or maintenance of remission in people with psoriasis. No time limit was placed on the literature search and there were no limitations duration of follow-up. However, the sample size had to be at least 25 participants per study arm and indirect populations were excluded.

The evidence considered included topical monotherapies compared with vitamin D or vitamin D analogue or with placebo/vehicle, while combined or concurrent vitamin D or vitamin D analogue and potent corticosteroid were compared with the constituent monotherapies (and not with placebo). Studies only comparing different dosages or formulations of the same intervention were excluded. Similarly, studies comparing interventions within the classes of either vitamin D and its analogues or corticosteroids were excluded (unless the comparison pertained to frequency of administration e.g., once or twice daily dosing). A class effect was assumed for these agents and so data on all vitamin D and its analogues was pooled into one analysis as was data on any potent corticosteroids and on very potent corticosteroids, unless heterogeneity was found.

The outcomes considered were:

- Clear/nearly clear or marked improvement (at least 75% improvement) on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)
- Clear/nearly clear or marked improvement (at least 75% improvement) on Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment
- Percentage change in PASI – change is represented by a negative value if the PASI score decreased
- Change in DLQI
- Duration of remission
- Time-to-remission or time-to-maximum effect based on IAGI, PGA, PASI or total severity score (to address part ii of the question)*
- Withdrawal due to toxicity
- Withdrawal due to lack of efficacy
- Skin atrophy

*For data on time-to-remission or time-to-maximum effect, absolute time-to-effect data or data from multiple time points in one study were reported as the first preference and graphical data were only included for interventions where such data were not available, or for long-term data not otherwise available. Additionally, data on IAGI, PGA, PAGI or PASI were reported in preference to TSS where available.

Fifty four RCTs were found that addressed the question and were included in the review [25,157-209]. However, just two studies[167,192,193] directly assessed maintenance treatment and just one study was conducted in a paediatric population[25].

A published Cochrane Review[210] was identified from the literature search, which at the time of development of this guideline was being updated and publication of which would not fall within the development period of this guideline. However, the original Cochrane Review was not able to be updated directly owing to differences in methodology and outcomes required to feed into a novel health economics model. The Cochrane reference list and literature search protocols were used for cross-referencing and the literature search was re-run to update it. Additionally, following close collaboration and discussion with the Cochrane Skin Group, study characteristic and withdrawal outcome data was extracted to enable novel meta analysis. The differed in terms of the disease severity and treatment duration (Table 61). Note the potential limitation of studies comparing interventions that act over different periods (e.g., the faster acting clobetasol propionate and the slower acting calcipotriol), especially if the treatment duration chosen for the trial does not permit the maximum effect of the slower acting intervention to be observed.

Table 61: Characteristics of included studies

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
Vitamin D or vitamin D analogues vs placebo				
HARRINGTON1996	Inclusion criteria: Stable plaque psoriasis Mean baseline modified PASI = 8.3 (range 0-59.4)	1. Calcipotriol 50 µg/g cream (BD)	8 weeks	Between patient
HIGHTON1995	Inclusion criteria: Moderate-to-severe chronic plaque psoriasis Mean baseline BSA: 9.1%	1. Calcipotriol 0.005% ointment (BD)	8 weeks	Between patient
ORANJE1997	Inclusion criteria: Mild-to-moderate (<30% BSA) Mean baseline severity not reported	1. Calcipotriol 50 µg/g ointment (BD)	8 weeks	Between patient Note: Children (age 2-14 years)
BARKER1999	Inclusion criteria: Stable plaque psoriasis covering <20% BSA Mean baseline severity score not reported	1. Calcipotriol 50 µg/g ointment (OD)	8 weeks	Within and between patient (between for our comparison)
DUBERTRET1992	Inclusion criteria: Unclear (symmetrical) Mean baseline PASI: 14.2	1. Calcipotriol 50 µg/g ointment (BD)	8 weeks (4 weeks randomised + 4 weeks preferred treatment)	Within patient
LANGER1992	Inclusion criteria: Severe chronic plaque psoriasis (symmetrical) Mean baseline severity score not reported	1. Calcitriol 3 µg/g ointment (BD)	6 weeks	Within patient
LANGER1993	Inclusion criteria: Severe chronic plaque psoriasis (symmetrical) Mean baseline global severity score: 3.5/4.0	1. Calcitriol 15 µg/g ointment (BD)	6 weeks	Within patient
PEREZ1996	Inclusion criteria: BSA ≥10% Mean total severity score at baseline:	1. Calcitriol 1.5 µg/g ointment (OD)	10 weeks	Within patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
	7.6 (range: 0-9)			
SCARPA1997	Inclusion criteria: Unclear – in- and out-patients (symmetrical) Mean baseline severity score not reported	1. Tacalcitol 4 µg/g ointment (OD)	6 weeks	Within patient
VANDERKERKHOF1996	Inclusion criteria: Stable plaque psoriasis Mean baseline BSA: 5.6%	1. Tacalcitol ointment, 4 µg/g (OD)	8 weeks (+4 weeks post-treatment follow-up)	Within patient
Potent corticosteroid vs placebo				
MEDANSKY1987	Inclusion criteria: total severity score ≥6 Mean baseline severity score not reported	1. Mometasone furoate ointment 0.1% (OD)	3 weeks	Between patient
KATZ1991	Inclusion criteria: Maintenance trial (in remission; initial severity ≤10% BSA) Mean baseline severity score not reported	1. Betamethasone dipropionate ointment (BD - intermittent)	24 weeks	Between patient
WORTZEL1975	Inclusion criteria: Moderately to very severe Mean baseline severity score not reported	1. Betamethasone dipropionate 0.05% ointment (BD)	3 weeks	Between patient
SEARS1997	Inclusion criteria: mild or moderate (TSS 3-8) Mean TSS at baseline: 6.0 (range 0-9)	1. Hydrocortisone butyrate 0.1% cream (BD)	3 weeks	Between patient
STEIN2001	Inclusion criteria: mild or moderate Mean TSS at baseline: 7.0 (range 0-12)	1. Betamethasone valerate 0.12% foam (BD)	12 weeks	Within patient
Very potent corticosteroid vs placebo				
BEUTNER2006	Inclusion criteria: Moderate to severe	1. Clobetasol propionate	4 weeks	Within patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
	Mean baseline severity score not reported	spray, 0.05% (BD)		
DECROIX2004	Inclusion criteria: Moderate-to-severe (BSA ≥10%) Mean baseline TSS: 8.4/12	1. Clobetasol propionate lotion, dose unclear (OD) 2. Clobetasol propionate cream, dose unclear (OD)	4 weeks	Between patient
GOTTLEIB2003C	Inclusion criteria: Mild to moderate (BSA <20%) Mean baseline BSA: 6.7%	1. Clobetasol propionate foam, 0.05% (BD)	2 weeks (+2 weeks post treatment follow-up)	Between patient
JARRATT2006	Inclusion criteria: BSA ≥2% (excluding scalp, face, groin and axillae) Mean baseline BSA: 7.7%	1. Clobetasol propionate spray, 0.05% (BD)	4 weeks (+ 4 week post-treatment follow-up)	Between patient
JORIZZO1997	Inclusion criteria: Moderate-to-severe (TSS ≥6/12) Mean baseline BSA: 8.1%	1. Clobetasol propionate emollient 0.05% (BD)	4 weeks (+2 week post-treatment follow-up)	Between patient
LEBWOHL2002	Inclusion criteria: Mild to moderate (TSS ≥3/12) Mean baseline severity score not reported	1. Clobetasol propionate foam, 0.05% (BD)	2 weeks (+2 weeks post treatment follow-up)	Between patient
LOWE2005	Inclusion criteria: Moderate-to-severe (TSS ≥6/12) Mean baseline TSS: 7.4/12	1. Clobetasol propionate lotion, 0.05% (BD) 2. Clobetasol propionate cream, 0.05% (BD)	4 weeks (+ 4 week post-treatment follow-up)	Between patient
OLSEN1996	Inclusion criteria: Moderate-to-severe (TSS ≥6/12) Mean baseline BSA: study 1 = 12%; study 2 = 13%	1. Fluticasone propionate ointment 0.005% (BD)	4 weeks	Between patient
Tazarotene vs placebo				
WEINSTEIN1996 AND	Inclusion criteria: BSA ≤20% Mean baseline BSA: 6.9±5.2%	1. Tazarotene 0.1% gel (OD) 2. Tazarotene 0.05% gel (OD)	12 weeks (+12 week post-treatment follow-up)	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
WEINSTEIN1997				
WEINSTEIN2003	Inclusion criteria: BSA ≥2% Mean baseline BSA: 10.5%	1. Tazarotene 0.1% cream (OD) 2. Tazarotene 0.05% cream (OD)	12 weeks (+12 week post-treatment follow-up)	Between patient
Vitamin D and vitamin D analogue vs potent corticosteroid				
BRUCE1994	Inclusion criteria: At least mild psoriasis (at least moderate plaque elevation) Mean baseline BSA coverage: 5-20%	1. Calcipotriol ointment, 0.005% (BD) 2. Fluocinonide 0.05% ointment (BD)	6 weeks	Between patient
CAMARASA2003	Inclusion criteria: Moderate to severe psoriasis (global severity score ≥ 2) Mean baseline PASI: 15.4 ± 10.6	1. Calcitriol 3 µg/g ointment (BD) 2. Betamethasone dipropionate 0.05% ointment (BD)	6 weeks	Between patient
CUNLIFFE1992	Inclusion criteria: stable plaque psoriasis Mean baseline PASI: 9.05	1. Calcipotriol 50 µg/g ointment (BD) 2. Betamethasone valerate 1 mg/g ointment (BD)	6 weeks	Between patient
MOLIN1997A	Inclusion criteria: Mild-to-moderate to psoriasis on limbs and/or trunk Mean baseline PASI: 58.1% had PASI <6, 30.5% had PASI 6-10.9 and 11.4% had PASI ≥11	1. Calcipotriol 50 µg/g cream (BD) 2. Betamethasone valerate 1 mg/g cream (BD)	8 weeks	Between patient
KRAGBALLE1991	Inclusion criteria: Unclear (symmetrical) Mean baseline PASI: 8.3	1. Calcipotriol 50 µg/g ointment (BD) 2. Betamethasone valerate 1 mg/g ointment (BD)	6 weeks	Within patient
Concurrent vitamin D or vitamin D analogue and corticosteroids (one applied in the morning and one in the evening) vs monotherapies				
KRAGBALLE1998	Inclusion criteria and mean baseline	1. Calcipotriol 50µg/g	8 weeks	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
	severity score unclear	(morning) + betamethasone valerate, 1 mg/g (evening) 2. Calcipotriol 50 µg/g ointment (BD) 3. Calcipotriol 50 µg/g ointment (OD)		
RUZICKA1998	Inclusion criteria: BSA ≤30% Mean baseline severity score not reported	1. 2 weeks calcipotriol 0.005% ointment (BD), then 4 weeks calcipotriol 0.005% ointment (morning) plus betamethasone valerate 0.1% ointment (evening) 2. 6 weeks calcipotriol 0.005% ointment (BD)	6 weeks (+ 8 weeks post-treatment follow-up)	Between patient
SALMHOFER2000	Inclusion criteria: <30% BSA (symmetrical) Mean baseline PASI: 5.5 ± 2.6	1. Calcipotriol 0.005% ointment (morning), plus diflucortolone valerate ointment 0.1% (evening) 2. Calcipotriol 0.005% µg/g ointment (BD)	4 weeks	Within patient
Combined vitamin D or vitamin D analogue and potent corticosteroids vs monotherapies				
DOUGLAS2002	Inclusion criteria: use of systemics Mean baseline modified PASI 10.7	1. Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment (BD) 2. Betamethasone dipropionate 0.5 mg/g ointment (BD) 3. Calcipotriol 50 µg/g ointment (BD)	4 weeks (+4 weeks post-treatment follow-up)	Between patient
FLEMING2010A	Inclusion criteria: At least mild Mean baseline PASI: 7.8	1. Calcipotriol 50 µg/g and betamethasone dipropionate	8 weeks	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
		0.5 mg/g gel (OD) 2. Calcipotriol 50 µg/g gel (OD) 3. Betamethasone dipropionate 0.5 mg/g gel (OD)		
GUENTHER2002	Inclusion criteria: At least 10% coverage of one or more body parts (arms, legs or trunk) Mean baseline PASI: 10.5	1. Calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g ointment (OD) 2. Calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g ointment (BD) 3. Calcipotriol 50 µg/g ointment (BD)	4 weeks	Between patient
KAUFMANN2002	Inclusion criteria: BSA ≥10% Mean baseline PASI: 10.0	1. Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment (OD) 2. Betamethasone dipropionate 0.5 mg/g ointment (OD) 3. Calcipotriol 50 µg/g ointment (OD)	4 weeks	Between patient
KRAGBALLE2004	Inclusion criteria: At least 10% coverage of one or more body parts (arms, legs or trunk) Mean baseline PASI: 10.5	1. Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment OD for 8 wks *then*: calcipotriol ointment 50 µg/g OD for 4 wks 2. Calcipotriol 50 µg/g and betamethasone dipropionate	12 weeks	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
		0.5 mg/g ointment OD for 4 wks *then*: calcipotriol ointment 50 µg/g OD (weekdays) and combined product containing calcipotriol monohydrate and betamethasone dipropionate OD (weekends) for 8 wks 3. Calcipotriol 50 µg/g ointment (BD)		
KRAGBALLE2006 AND KRAGBALLE2006A	Inclusion criteria: At least moderate on PGA Mean baseline severity score not reported (69% moderate)	1. Calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g ointment (OD) 2. Calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g ointment (OD) alternating with calcipotriol 50 µg/g ointment (OD) 3. 4 weeks of calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g ointment (OD) *then:* 48 weeks calcipotriol 50 µg/g ointment (OD)	52 weeks	Between patient
LANGLEY2011A	Inclusion criteria: At least 10% of arms and/or legs and/or trunk; at least moderate on PGA Mean baseline: PASI 9.39	1. Calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g gel (OD) 2. Tacalcitol 4 µg/g ointment (OD)	8 weeks	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
ORTONNE2004	Inclusion criteria: stable plaque psoriasis Mean baseline: PASI 9.8	1. Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g ointment (OD) for 4 weeks *then* calcipotriol 50 µg/g ointment (OD) for 4 weeks 2. Tacalcitol 4 µg/g ointment (OD) for 8 weeks	8 weeks	Between patient
PAPP2003	Inclusion criteria: BSA ≥10% Mean baseline PASI: 10.8	1. Calcipotriol 50 µg/g ointment and betamethasone dipropionate 0.5 mg/g ointment (BD) 2. Calcipotriol 50 µg/g ointment (BD) 3. Betamethasone dipropionate 0.5 mg/g ointment (BD)	4 weeks	Between patient
SARACENO2007	Inclusion criteria: Mild-to-moderate Mean baseline PASI: 9.2	1. Calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g cream (OD) for 4 weeks *then* calcipotriol 50 µg/g cream (BD) for 8 weeks 2. Calcipotriol 50 µg/g cream (BD) for 12 weeks	12 weeks	Between patient
Dithranol vs vitamin D or vitamin D analogue				
BERTHJONES1992	Inclusion criteria: out-patients Mean baseline PASI: 9.3	1. Calcipotriol 50 µg/g ointment (BD) 2. Dithranol 0.1-2.0% cream (OD)	8 weeks	Between patient
CHRISTIENSEN1999	Inclusion criteria: Mild to severe	1. Calcipotriol 50 µg/g	8 weeks	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
	(≤10% BSA) Mean baseline TSS: 6.24 (range 0-9)	ointment (BD) 2. Dithranol 1-3% cream (OD)		
HUTCHINSON2000	Inclusion criteria: At least moderate Mean baseline PASI: 11.8	1. Calcitriol 3 µg/g ointment (BD) 2. Dithranol 0.25-2.0% cream (OD for 30 mins)	8 weeks	Between patient
VANDERKERKHOF2006	Inclusion criteria: in at least 1 body region Mean baseline PASI: 9.9	1. Calcipotriol 50 µg/g ointment (BD) 2. Dithranol 0.05-5.0% cream (OD)	8 weeks	Between patient
WALL1998	Inclusion criteria: Mild to moderate (≥100 cm^2 surface area; <40% BSA) Mean baseline severity score not reported	1. Calcipotriol 0.005% ointment (BD) 2. Dithranol 0.1-2.0% cream (OD)	3 months	Between patient
Coal tar vs vitamin D or vitamin D analogue				
ALORAPALLI2010	Inclusion criteria: 3-15% BSA (excluding head, groin, palms and soles) Mean baseline PASI: 7.1	1. Liquor carbonis distillate (15%, equivalent to 2.3% coal tar) solution (BD) 2. Calcipotriol 0.005% cream (BD)	12 weeks (+6 weeks post-treatment follow-up)	Between patient
PINHEIRO1997	Inclusion criteria: BSA ≥100 cm^2 Mean baseline severity score not reported	1. Coal tar 5% cream (BD) 2. Calcipotriol 50 µg/g ointment (BD)	8 weeks	Between patient
THAM1994	Inclusion criteria: unclear (symmetrical) Mean baseline modified PASI 6.65 out of 64.8	1. Liquor picis carbonis 15% coal tar cream (OD) 2. Calcipotriol 50 µg/g ointment (BD)	6 weeks (+4 weeks preferred treatment phase)	Within patient
Potent corticosteroid vs tar (for time-to-maximum response data)				
THAWORNCHAISIT2007	Inclusion criteria: Mild to moderate Mean baseline PASI: 17.4	1. Liquor carbonis detergens 10% coal tar cream (BD)	6 weeks	Between patient

Reference ID	Disease severity	Active intervention(s) – dose, formulation and frequency	Maximum treatment duration	Unit of randomisation
		2. Betamethasone valerate 0.1% cream (BD)		

1

Data from within-patient trials should be adjusted for the correlation coefficient relating to the comparison of paired data. None of the included studies reported this statistic; neither did they report sufficient detail for it to be calculated. Where possible, within- and between-patient data were pooled, accepting that this may result in underweighting of the within-patient studies. This is a conservative estimate. Sensitivity analyses were undertaken to investigate whether the effect size varied consistently for within- and between-patient studies. There was no evidence that the size of effect varied in a systematic way and it was often not possible to say if consistent differences were present as there was only one within patient study for a given comparison.

8.1.2 Vitamin D and vitamin D analogue vs. placebo

8.1.2.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and vitamin D analogues	placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol OD (follow-up 4-8 weeks)											
3 Barker1999 Fleming2010A Kaufmann2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129/587 (22%)	17/223 (7.6%)	RR 2.78 (1.75 to 4.41)	136 more per 1000 (from 57 more to 260 more)	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Calcipotriol BD (follow-up 4-8 weeks)											
4 Dubertret 1992 Guenther 2002 Highton 1995 Papp 2003	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	351/721 (48.7%)	61/498 (12.2%)	RR 4.48 (3.5 to 5.73)	426 more per 1000 (from 306 more to 579 more)	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Calcitriol OD (follow-up 10 weeks)											
1 Perez 1996	randomised trials	serious[c]	no serious inconsistency	no serious indirectness[d]	no serious imprecision	none	37/84 (44%)	0/84 (0%)	RR 75 (4.68 to 1201.67)	-	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Calcitriol BD (follow-up 6 weeks)											
2 Langner 1992 Langner 1993	randomised trials	serious[e]	no serious inconsistency	serious[f]	no serious imprecision	none	45/61 (73.8%)	22/61 (36.1%)	RR 2.05 (1.42 to 2.95)	379 more per 1000 (from 151 more to 703 more)	⊕⊕OO LOW
Investigator's assessment (clear/nearly clear) - Tacalcitol (OD) (follow-up 8 weeks)											
1 Langley 2011A	randomised trials	very serious[g]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/184 (17.9%)	5/91 (5.5%)	RR 3.26 (1.32 to 8.08)	124 more per 1000 (from 18 more to 389 more)	⊕⊕OO LOW

Patient's assessment (clear/nearly clear) - Calcipotriol OD or BD (follow-up 4-8 weeks)											
3 Kaufmann 2002 Guenther 2002 Harrington 1996	randomised trials	serious[h]	no serious inconsistency	no serious indirectness	no serious imprecision	none	402/988 (40.7%)	54/434 (12.4%)	RR 3.35 (2.58 to 4.34)	292 more per 1000 (from 197 more to 416 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) - Tacalcitol (OD) (follow-up 8 weeks)											
1 Langley 2011A	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	very serious[j]	none	35/163 (21.5%)	14/64 (21.9%)	RR 0.98 (0.57 to 1.7)	4 fewer per 1000 (from 94 fewer to 153 more)	⊕OOO VERY LOW
% change in PASI - Calcipotriol BD (follow-up 4 weeks) (Better indicated by lower values)											
1 Dubertret 1992	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	60	-	MD 23.2 lower (35.57 to 10.83 lower)	⊕⊕⊕O MODERATE
Withdrawals due to adverse events – Calcipotriol, calcitriol or tacalcitol OD or BD (follow-up 4-8 weeks)											
11 Barker 1999 Kaufmann 2002 Guenther 2002 Harrington 1996 Highton 1995 Langner 1992 Langner 1993 Langley 2011A Perez 1996 Scarpa 1997 van der Kerkhof 1996	randomised trials[k]	serious[l]	no serious inconsistency	no serious indirectness[m]	serious[n]	data	40/1736 (2.3%)	31/1055 (2.9%)	RR 0.62 (0.4 to 0.97)	11 fewer per 1000 (from 1 fewer to 18 fewer)	⊕⊕OO LOW
Withdrawals due to lack of efficacy – Calcipotriol or calcitriol OD or BD (follow-up 4-8 weeks)											
7 Barker 1999 Guenther 2002 Harrington 1996 Langner 1992 Langner 1993 Perez 1996 Scarpa 1997	randomised trials[o]	serious[p]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/893 (0.34%)	22/644 (3.4%)	RR 0.15 (0.05 to 0.42)	29 fewer per 1000 (from 20 fewer to 32 fewer)	⊕⊕⊕O MODERATE
Skin atrophy – Calcipotriol BD (follow-up 4 weeks)											

2 Guenther 2002 Papp 2003	randomised trials	serious[q]	no serious inconsistency	no serious indirectness	very serious[j]	none	1/535 (0.19%)	1/316 (0.32%)	RR 0.92 (0.06 to 14.56)	0 fewer per 1000 (from 3 fewer to 43 more)	⊕OOO VERY LOW
Relapse rate at 8 weeks post-treatment - Tacalcitol OD (follow-up 8 weeks)											
1 Langley 2011A	randomised trials	very serious[r]	no serious inconsistency	serious[s]	serious[n]	none	7/31 (22.6%)	3/5 (60%)	RR 0.38 (0.14 to 0.99)	372 fewer per 1000 (from 6 fewer to 516 fewer)	⊕OOO VERY LOW
Median time to relapse - Tacalcitol OD (follow-up 8 weeks post treatment)											
1 Langley 2011A	randomised trials	very serious[r]	no serious inconsistency	no serious indirectness	serious[t]	none	31	5	-	61 days in both groups	⊕OOO VERY LOW

(a) 3/3 unclear allocation concealment; 1/3 (93.4% weighted) differential dropout (8.1%: calcipotriol; 15.9%: vehicle); 1/3 (4% weighted) baseline clinical characteristics not reported
(b) 4/4 unclear allocation concealment; 2/4 unclear blinding; 1/4 (35% weighted) unclear if dropout rate was evenly distributed between study arms
(c) Unclear allocation concealment and blinding
(d) Study used Vaseline as the placebo (not vehicle)
(e) 2/2 unclear allocation concealment and blinding; 1/2 studies (40.9% weighted) treatment stopped if at least one side cleared; therefore, lesion on contra lateral side may have clear if treated for the full study period
(f) 1/2 studies used high concentration of calcitriol (15 µg/g, licensed at 3 µg/g)
(g) Unclear allocation concealment and blinding; high differential dropout rate: 11.4% tacalcitol; 29.7% placebo
(h) 3/3 unclear allocation concealment; 2/3 studies (61.4% weighted) higher but acceptable dropout in vehicle group
(i) Unclear allocation concealment and single blinded (investigator); high dropout rate in placebo group (tacalcitol: 11.4%; placebo: 29.7%
(j) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(k) For 3/9 (Barker, Scarpa and vander Kerkhof) studies data were taken from a published Cochrane Review
(l) 10/11 unclear allocation concealment; 3/11 unclear blinding (20.6% weighted); 3/11 higher dropout rate in placebo group; 1/11 (3.4% weighted) unclear baseline clinical characteristics
(m) In one study (weighted 1.1%) 24.6% of patients test lesions were localised on the face or face and other parts of the body; one study used a very high concentration of calcitriol (weighted 1.1%)
(n) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(o) For 1/4 studies (Barker) data were taken from a published Cochrane Review
(p) 7/7 unclear allocation concealment; 1/7 (6.1% weighted) unclear baseline clinical characteristics; 1/7 (9.7% weighted) higher dropout in placebo group
(q) 2/2 unclear allocation concealment
(r) Unclear allocation concealment and single blinded (investigator); high dropout rate in placebo group (tacalcitol: 11.4%; placebo: 29.7%); also, unclear baseline comparability as only includes those in each group who achieved remission; therefore, there are fewer participants in the placebo group
(s) Surrogate outcome for duration of remission
(t) No range provided

8.1.2.2 Evidence statements

In people with psoriasis, topical vitamin D or vitamin D analogue treatment was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear on PGA) at 4-10 weeks for calcipotriol once daily, calcipotriol twice daily, calcitriol once daily, calcitriol twice daily or tacalcitol once daily [11 studies (7 between- and 4 within-patient studies); 2387 participants (2594 randomised units); low to moderate quality evidence][158,163,166,169,184,185,189,194,195,200,201]
- Patient assessment (clear/nearly clear on PGA) at 4-8 weeks for calcipotriol once daily or calcipotriol twice daily [3 between-patient studies; 1432 participants; moderate quality evidence][165,185,189]
- Percentage change in PASI at 4 weeks for calcipotriol twice daily [1 within-patient study; 60 participants (120 randomised units); moderate quality evidence][163]
- Withdrawal due to adverse events at 4-8 weeks [11 studies (6 between- and 5 within-patient); 2367 participants (2791 randomised units); low quality evidence] [158,165,166,169,185,189,194,195,201,204]
- Withdrawal due to lack of efficacy at 4-8 weeks [7 studies (4 between- and 3 within-patient); 1207 participants (1477 randomised units); moderate quality evidence][158,165,185,194,195,201,204]
- Relapse at 8 weeks post treatment with tacalcitol once daily [1 between-patient study; 36 participants; very low quality evidence][169].

In people with psoriasis, there was no statistically significant difference between topical vitamin D or vitamin D analogue treatment and placebo for:

- Patient assessment at 8 weeks (clear/nearly clear) with tacalcitol once daily [1 between-patient study; 227 participants; very low quality evidence][169]
- Skin atrophy at 4 weeks for calcipotriol twice daily [2 between-patient studies; 851 participants; very low quality evidence][185,200]

Evidence statement for individual study where no statistical analysis could be performed

In people with psoriasis, there was no difference between topical vitamin D or vitamin D analogue treatment and placebo for:

- Median time-to-relapse among those who had achieved remission with tacalcitol once daily (followed for up to 8 weeks post treatment) [1 study; 36 participants; very low quality evidence][169].

8.1.2.3 Heterogeneity

- There was significant heterogeneity between data regarding the investigator's assessment of efficacy. This heterogeneity was removed by creating subgroups based on the specific agent and treatment frequency of the vitamin D or vitamin D analogue. Nevertheless, all agents and frequencies demonstrated a clinically significant benefit compared with placebo.
- There was significant heterogeneity between data regarding the patient's assessment of efficacy. This heterogeneity was removed by creating subgroups based on the specific agent within the vitamin D or vitamin D analogue class, while treatment frequency did not explain the differences. It appeared that

tacalcitol was not more effective than placebo based on patient's assessment, whereas calcipotriol was more effective. However, the heterogeneity may also have been caused by the tacalcitol study having a higher risk of bias as it was only investigator blinded (although this may be more likely to increase the effect estimate in favour of the active intervention) and had a 30% drop-out rate in the placebo group.

- There was no significant heterogeneity for the remaining outcomes

8.1.3 Vitamin D or vitamin D analogue vs. placebo (children)

8.1.3.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogues	placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol BD (follow-up 8 weeks)											
1 Oranje 1997	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	26/43 (60.5%)	15/34 (44.1%)	RR 1.37 (0.87 to 2.15)	163 more per 1000 (from 57 fewer to 507 more)	⊕⊕OO LOW
Patient's assessment (clear/nearly clear) - Calcipotriol BD (follow-up 8 weeks)											
1 Oranje 1997	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	21/43 (48.8%)	16/34 (47.1%)	RR 1.04 (0.65 to 1.66)	19 more per 1000 (from 165 fewer to 311 more)	⊕OOO VERY LOW
% change in PASI - Calcipotriol BD (follow-up 8 weeks)											
1 Oranje 1997	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	43	34	-	MD 14.90 lower (34.69 lower to 4.89 higher)	⊕⊕OO LOW

(a) Unclear allocation concealment and blinding; acceptable drop-out rates but higher with calcipotriol
(b) Confidence interval ranges from clinically significant effect to no effect
(c) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.1.3.2 Evidence statements

In children with psoriasis, there was no statistically significant difference between calcipotriol twice daily and placebo for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [1 between-patient study; 77 participants; low quality evidence][25]
- Patients assessment (clear/nearly clear) at 8 weeks [1 between-patient study; 77 participants; very low quality evidence][25]
- % change in PASI at 8 weeks [1 between-patient study; 77 participants; low quality evidence][25]

8.1.3.3 Heterogeneity

- Not applicable as only one study assessed vitamin D or vitamin D analogues compared with placebo in children

8.1.4 Potent corticosteroid vs. placebo

8.1.4.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid (potent)	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – Mometasone furoate OD, hydrocortisone butyrate BD, betamethasone dipropionate OD or BD (follow-up 3-8 weeks)											
6 Fleming2010A Kaufmann 2002 Papp 2003 Wortzel 1975 Medansky 1987 Sears 1997	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	409/1038 (39.4%)	36/469 (7.7%)	RR 4.68 (3.38 to 6.48)	282 more per 1000 (from 183 more to 421 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) – hydrocortisone butyrate BD or betamethasone dipropionate OD (follow-up 3-4 weeks)											
2 Kaufmann 2002 Sears 1997	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	228/554 (41.2%)	17/240 (7.1%)	RR 4.88 (3.06 to 7.77)	275 more per 1000 (from 146 more to 480 more)	⊕⊕⊕O MODERATE
Withdrawals due to adverse events - Once daily potent corticosteroid (mometasone furoate or betamethasone dipropionate) (follow-up 3-4 weeks)											

2 Kaufmann 2002 Medansky 1987	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/502 (1%)	15/191 (7.9%)	RR 0.13 (0.05 to 0.36)	68 fewer per 1000 (from 50 fewer to 75 fewer)	⊕⊕⊕O MODERATE
Withdrawals due to adverse events - Twice daily potent corticosteroid (hydrocortisone butyrate, betamethasone valerate or betamethasone dipropionate) (follow-up 3-12 weeks)											
3 Sears 1997 Stein 2001 Wortzel 1975	randomised trials	serious[d]	no serious inconsistency	no serious indirectness[e]	very serious[f]	none	4/163 (2.5%)	0/162 (0%)	RR 5.02 (0.6 to 42.26)	-	⊕OOO VERY LOW
Withdrawals due to lack of efficacy - Betamethasone dipropionate BD (follow-up 3 weeks)											
1 Wortzel 1975	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/39 (0%)	0/37 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH
Skin atrophy – Mometasone furoate OD or betamethasone dipropionate BD (follow-up 3-4 weeks)											
2 Papp 2003 Medansky 1987	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	very serious[f]	none	2/363 (0.55%)	0/153 (0%)	RR 1.74 (0.08 to 35.87)	-	⊕OOO VERY LOW

(a) 5/6 unclear allocation concealment; 2/6 unclear blinding; 1/6 high dropout rate (weighted 15%); 1/6 (49% weighted) differential dropout rate: 4.6% betamethasone, 15.9% placebo
(b) Unclear allocation concealment and blinding
(c) 2/2 unclear allocation concealment; 1/2 unclear blinding; 1/2 (16.5% weighted) high dropout rate (21.5% from steroid and 26.3% from placebo)
(d) 1/3 inadequate and 1/3 unclear allocation concealment; 2/3 unclear blinding
(e) Data for Stein study taken from published Cochrane Review
(f) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(g) 2/2 unclear allocation concealment; 1/2 (0% weighted) unclear blinding and high dropout rate (21.5% corticosteroids and 26.3% placebo)

8.1.4.2 Evidence statements

In people with psoriasis, topical potent corticosteroid treatment was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 3-8 weeks for mometasone furoate once daily, hydrocortisone butyrate twice daily and betamethasone dipropionate once or twice daily [6 between-patient studies; 1507 participants; moderate quality evidence][170,174,184,189,200,209]
- Patient's assessment (clear/nearly clear) at 3-4 weeks for hydrocortisone butyrate twice daily or betamethasone dipropionate once daily [2 between-patient studies; 794 participants; moderate quality evidence][174,189]
- Withdrawal due to adverse events at 3-4 weeks for potent corticosteroid (mometasone furoate or betamethasone dipropionate) once daily [2 between-patient studies; 693 participants; moderate quality evidence][170,189]

In people with psoriasis, there were no events with either topical potent corticosteroid treatment or placebo for:

- Withdrawal due to lack of efficacy at 3 weeks for betamethasone dipropionate twice daily [1 between-patient study; 76 participants; high quality evidence][209]

In people with psoriasis, there was no statistically significant difference between topical potent corticosteroid treatment and placebo for:

- Withdrawal due to adverse events at 3-12 weeks for potent corticosteroid (hydrocortisone butyrate, betamethasone valerate or betamethasone dipropionate) twice daily [3 studies (2 between- and 1 within-patient); 285 participants (325 randomised units); very low quality evidence][174,175,209]
- Skin atrophy [2 between-patient studies; 516 participants; very low quality evidence][170,200]

8.1.4.3 Heterogeneity

- There was significant heterogeneity between data regarding withdrawals due to adverse effects. This heterogeneity was removed by creating subgroups based on treatment frequency. It was considered clinically more likely that the treatment frequency was causing the heterogeneity rather than the specific agent within the potent corticosteroid class.
- There was no significant heterogeneity for the remaining outcomes

8.1.5 Very potent corticosteroid vs. placebo

8.1.5.1 Evidence profile

Quality assessment	No of patients	Effect	Quality

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Corticosteroid (very potent)**	**placebo**	**Relative (95% CI)**	**Absolute**	
Investigator's assessment (clear/nearly clear) – clobetasol propionate OD or BD (follow-up 2-4 weeks)											
5 Decroix 2004 Gottlieb 2003C Jarratt 2006 Lebwohl 2002 Lowe 2005	randomised trials	very serious[a]	serious[b]	no serious indirectness	no serious imprecision	None	370/592 (62.5%)	35/267 (13.1%)	RR 6.45 (2.63 to 15.81)	714 more per 1000 (from 214 more to 1000 more)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) - Clobetasol propionate BD (follow-up 2 weeks)											
2 Gottlieb 2003C Lebwohl 2002	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	None	87/200 (43.5%)	37/160 (23.1%)	RR 2.23 (1.62 to 3.05)	284 more per 1000 (from 143 more to 474 more)	⊕⊕OO LOW
Withdrawals due to adverse events – clobetasol propionate OD or BD (follow-up 2-4 weeks)											
7 Beutner 2006 Decroix 2004 Gottlieb 2003C Jarratt 2006 Jorizzo 1997 Lebwohl 2002 Lowe 2005	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	None	3/653 (0.46%)	2/331 (0.60%)	RR 0.56 (0.12 to 2.52)	4 fewer per 1000 (from 8 fewer to 13 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy - Clobetasol propionate OD or BD (follow-up 4 weeks)											
3 Decroix 2004 Beutner 2006 Jarratt 2006	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	very serious[e]	None	0/268 (0%)	1/117 (0.85%)	RR 0.06 (0 to 1.44)	8 fewer per 1000 (from 5 fewer to 9 more)	⊕OOO VERY LOW
Skin atrophy - Clobetasol propionate OD or BD (follow-up 4 weeks)											
4 Beutner 2006 Decroix 2004 Jarratt 2006 Jorizzo 1997	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	very serious[e]	None	7/308 (2.3%)	0/156 (0%)	RR 2.7 (0.16 to 46.15)	-	⊕OOO VERY LOW

(a) 5/5 unclear allocation concealment; 3/5 unclear blinding; 2/5 single blind (investigator); 1/5 (2.1% weighted) high dropout rate: 27.6% in placebo group, 6.1% and 4.9% in clobetasol lotion and cream; 1/5 (67.3% weighted) unclear baseline demographics; 1/5 (21.7% weighted) fewer males in clobetasol group

(b) Heterogeneity was present (I^2 = 70%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect)

(c) 2/2 unclear allocation concealment and blinding; 1/2 (96% weighted) unclear baseline demographics

(d) 7/7 unclear allocation concealment; 5/7 unclear blinding and 2/7 single blinded (investigator); 1/7 (35.6% weighted) unclear baseline demographics; 2/7 (44% weighted) high differential dropout rate

(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

(f) 3/3 unclear allocation concealment; 2/3 unclear blinding and 1/3 single blind (investigator)

(g) 4/4 unclear allocation concealment; 3/4 unclear blinding and 1/4 single blind (investigator)

8.1.5.2 Evidence statements

In people with psoriasis, topical very potent corticosteroid treatment was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear)at 2-4 weeks for clobetasol propionate once or twice daily [5 between-patient studies; 859 participants; very low quality evidence][164,182,187,196,197]
- Patient's assessment (clear/nearly clear) at 2 weeks for clobetasol propionate twice daily [2 between-patient studies; 124 participants; low quality evidence][164,196]

In people with psoriasis, there was no statistically significant difference between topical very potent corticosteroid treatment and placebo for:

- Withdrawal due to adverse events at 2-4 weeks for clobetasol propionate once or twice daily [7 between-patient studies; 984 participants; very low quality evidence][160,164,182,187,188,196,197]
- Withdrawal due to lack of efficacy at 4 weeks for clobetasol propionate once or twice daily [3 studies (2 between- and 1 within-patient); 360 participants (385 randomised units); very low quality evidence][160,182,187]
- Skin atrophy at 4 weeks for clobetasol propionate once or twice daily [4 studies (3 between- and 1 within-patient); 439 participants (464 randomised units); very low quality evidence][160,182,187,188]

8.1.5.3 Heterogeneity

- For the outcome of investigator's assessment of achieving clear/nearly clear status high heterogeneity was present between the results for the five studies. The heterogeneity could not be explained by any of the pre-specified subgroups for investigation or by excluding studies at high/very high risk of bias. It is likely to be caused by the small size of three of the studies[187,196,197]. The two sufficiently powered studies demonstrated a clear clinical benefit of very potent steroids compared with placebo.
- There was no significant heterogeneity for the remaining outcomes

8.1.6 Tazarotene vs. placebo

8.1.6.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tazarotene	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – Tazarotene OD (follow-up 12 weeks)											
2[a] Weinstein 2003	randomised trials	very serious[b]	serious[c]	no serious indirectness	serious[d]	none	50/860 (5.8%)	9/443 (2%)	RR 3.03 (0.83 to 11.07)	41 more per 1000 (from 3 fewer to 205 more)	⊕OOO VERY LOW
Withdrawals due to adverse events – Tazarotene OD (follow-up 12 weeks)											
3[a] Weinstein 2003 Weinstein 1996	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/1046 (10.7%)	23/527 (4.4%)	RR 2.45 (1.58 to 3.8)	63 more per 1000 (from 25 more to 122 more)	⊕⊕OO LOW
Withdrawals due to lack of efficacy – Tazarotene OD (follow-up 12 weeks)											
1 Weinstein 1996	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	very serious[g]	none	9/216 (4.2%)	6/108 (5.6%)	RR 0.75 (0.27 to 2.05)	14 fewer per 1000 (from 41 fewer to 58 more)	⊕OOO VERY LOW
Skin atrophy – Tazarotene OD (follow-up 12 weeks)											
1 Weinstein 1996	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/216 (0%)	0/108 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE

(a) Two studies reported within one publication
(b) 2/2 unclear allocation concealment and blinding; 2/2 high drop-out rate (tazarotene: 38.5% and 36.6%; placebo: 32.2% and 23.8%)
(c) Heterogeneity was present (I^2 = 61%) that could not be explained by pre-defined subgroups (however, both studies showed the same direction of effect)
(d) Confidence interval ranges from clinically important effect to no effect
(e) 3/3 unclear allocation concealment; 2/3 (weighted 47.4 and 39.1%) unclear blinding and high drop-out rate (tazarotene: 38.5% and 36.6%; placebo: 32.2% and 23.8%)
(f) Unclear allocation concealment
(g) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

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8.1.6.2 Evidence statements

In people with psoriasis, placebo was statistically significantly better than tazarotene applied once daily for:

- Withdrawal due to adverse events at 12 weeks [3 between-patient studies; 1573 participants; low quality evidence] [178,179,208]

In people with psoriasis, there were no events with either tazarotene or placebo for:

- Skin atrophy at 12 weeks [1 between-patient study; 324 participants; moderate quality evidence][178,179]

In people with psoriasis, there was no statistically significant difference between tazarotene and placebo applied once daily for:

- Investigator's assessment (clear/nearly clear) at 12 weeks [2 between-patient studies; 1303 participants; very low quality evidence][208]
- Withdrawal due to lack of efficacy at 12 weeks [1 between-patient study; 324 participants; very low quality evidence][178,179]

8.1.6.3 Subgroups and heterogeneity

- For the outcome of investigator's assessment of achieving clear/nearly clear status heterogeneity was present between the results. The heterogeneity could not be explained by any of the pre-specified subgroups for investigation or excluding studies at high risk of bias.
- There was no significant heterogeneity for the remaining outcomes

8.1.7 Potent corticosteroid vs. placebo for maintenance of remission

This study included participants who achieved remission after 3-4 weeks treatment with betamethasone dipropionate (remission defined as: erythema score ≤ 1 (slight or minimal); induration = 0.5 (none-slight); scaling = 0 (none)). The maintenance regimen for those in remission and randomised to active treatment was intermittent betamethasone dipropionate applied to the site of the healed lesion (three consecutive applications 12 hours apart, once a week for a maximum treatment period of 6 months).

8.1.7.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid (potent)	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (maintaining clear/slight) – intermittent betamethasone dipropionate BD (follow-up 24 weeks)											
1 Katz 1991	randomised trials	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	27/46 (58.7%)	7/44 (15.9%)	RR 3.69 (1.79 to 7.59)	428 more per 1000 (from 126 more to 1000 more)	⊕⊕OO LOW
Time-to-relapse – intermittent betamethasone dipropionate BD (follow-up 24 weeks)											
1 Katz 1991	randomised trials	serious[a]	no serious inconsistency	serious[c]	no serious imprecision	none	16/46 (34.8%)	35/44 (79.5%)	HR 0.37 (0.21 to 0.67)	351 fewer per 1000 (from 141 fewer to 512 fewer)	⊕⊕OO LOW
Withdrawals due to adverse events – intermittent betamethasone dipropionate BD (follow-up 24 weeks)											
1 Katz 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/44 (0%)	0/42 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Skin atrophy – intermittent betamethasone dipropionate BD (follow-up 24 weeks)											
1 Katz 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/46 (0%)	0/44 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE

(a) Unclear allocation concealment and blinding
(b) Definition of response does not match the review criteria for clear/nearly clear (broader - clear or slight on a 4-point scale; clear, slight, moderate, severe) and so may overestimate efficacy
(c) Definition of relapse includes failure just at target plaques or in overall disease status

8.1.7.2 Evidence statements

In people with psoriasis, intermittent twice daily topical potent corticosteroid (betamethasone dipropionate) was statistically significantly better than placebo for the maintenance of remission for:

- Investigator's assessment (clear/slight) at 24 weeks [1 between-patient study; 90 participants; low quality evidence][167]
- Time-to-relapse after a maximum follow-up of at 24 weeks [1 between-patient study; 90 participants; low quality evidence][167]

In people with psoriasis, there were no events with either intermittent twice daily topical potent corticosteroid (betamethasone dipropionate) or placebo for the maintenance of remission for:

- Withdrawal due to adverse events at 24 weeks [1 between-patient study; 86 participants; moderate quality evidence][167]
- Skin atrophy at 24 weeks [1 between-patient study; 90 participants; moderate quality evidence][167]

8.1.7.3 Heterogeneity

Not applicable as only one study assessed potent corticosteroid compared with placebo for the maintenance of remission.

8.1.8 Vitamin D or vitamin D analogue vs. potent corticosteroid

8.1.8.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Vitamin D or	Corticosteroid	Relative	Absolute	

		bias				considerations	vitamin D analogues	(potent)	(95% CI)		
Investigator's assessment (clear/nearly clear) – Calcipotriol OD/BD or calcitriol BD vs betamethasone dipropionate OD/BD or betamethasone valerate BD (follow-up 4-8 weeks)											
6 Fleming 2010A Kaufmann 2002 Douglas 2002 Papp 2003 Molin 1997 Camarasa 2003	randomised trials	serious[a]	very serious[b]	no serious indirectness	serious[c]	none	547/1565 (35%)	730/1571 (46.5%)	RR 0.76 (0.62 to 0.94)	122 fewer per 1000 (from 28 fewer to 177 fewer)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) - Calcipotriol OD vs betamethasone dipropionate OD (follow-up 4 weeks)											
1 Kaufmann 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/480 (28.5%)	216/476 (45.4%)	RR 0.63 (0.53 to 0.75)	168 fewer per 1000 (from 113 fewer to 213 fewer)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) - Calcipotriol BD vs betamethasone dipropionate BD (follow-up 4 weeks)											
1 Douglas 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[c]	none	140/365 (38.4%)	183/363 (50.4%)	RR 0.76 (0.64 to 0.9)	121 fewer per 1000 (from 50 fewer to 181 fewer)	⊕⊕OO LOW
Patient's assessment (clear/nearly clear) - Calcipotriol BD vs betamethasone valerate BD (follow-up 6 weeks)											
2 Cunliffe 1992 Kragballe 1991	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[c]	none	403/543 (61.2%)	338/542 (50.5%)	RR 1.19 (1.10 to 1.29)	118 more per 1000 (from 62 more to 181 more)	⊕⊕OO LOW
% change in PASI - Calcipotriol (BD) vs betamethasone valerate (BD) (follow-up 6-8 weeks; Better indicated by lower values)											
2 Kragballe 1991 Molin 1997	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	547	549	-	MD 5.94 higher (2.29 to 9.60 higher)	⊕⊕⊕O MODERATE
Relapse rate (requiring re-treatment [not maintaining clear/nearly clear] within 8-weeks post Tx) - Calcitriol BD vs betamethasone dipropionate BD											
1 Camarasa 2003	randomised trials	very serious[f]	no serious inconsistency	serious[g]	serious[h]	none	30/58 (51.7%)	55/73 (75.3%)	RR 0.69 (0.52 to 0.91)	234 fewer per 1000 (from 68 fewer to 362 fewer)	⊕OOO VERY LOW
Mean time to relapse (requiring re-treatment [not maintaining clear/nearly clear] within 8-weeks post Tx) - Calcitriol BD vs betamethasone dipropionate BD											
1	randomised	very	no serious	no serious	serious[i]	none	58	73	-	Vitamin D: 25.3 days	⊕OOO

Camarasa 2003	trials	serious[f]	inconsistency	indirectness						Corticosteroid: 23.4 days	VERY LOW
Withdrawals due to adverse events – Calcipotriol OD/BD or calcitriol BD vs betamethasone dipropionate OD/BD, betamethasone valerate BD or fluocinonide BD (follow-up 4-8 weeks)											
7 Douglas 2002 Kaufmann 2002 Cunliffe 1992 Kragballe 1991 Molin 1997 Bruce 1994 Camarasa 2003	randomised trials	serious[j]	no serious inconsistency[k]	no serious indirectness	serious[c]	none	30/1709 (1.8%)	14/1718 (0.81%)	RR 2.10 (1.13 to 3.90)	9 more per 1000 (from 1 more to 24 more)	⊕⊕OO LOW
Withdrawals due to lack of efficacy – Calcipotriol or calcitriol BD vs betamethasone dipropionate or valerate BD (follow-up 6 weeks)											
3 Cunliffe 1992 Kragballe 1991 Camarasa 2003	randomised trials	serious[l]	no serious inconsistency[m]	no serious indirectness	very serious[n]	none	11/661 (1.7%)	11/660 (1.7%)	RR 1 (0.44 to 2.28)	0 fewer per 1000 (from 9 fewer to 21 more)	⊕OOO VERY LOW
Skin atrophy – Calcipotriol BD vs betamethasone dipropionate or valerate BD (follow-up 4-8 weeks)											
2 Papp 2003 Molin 1997	randomised trials	serious[o]	no serious inconsistency	no serious indirectness	very serious[n]	none	0/515 (0%)	5/523 (0.96%)	RR 0.17 (0.02 to 1.4)	8 fewer per 1000 (from 9 fewer to 4 more)	⊕OOO VERY LOW

(a) 6/6 unclear allocation concealment; 2/6 (26.8% weighted) unclear blinding
(b) Heterogeneity was present (I^2 = 81%) that could not be explained by pre-defined subgroups (however, 5/6 studies showed the same direction of effect)
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit in favour of corticosteroid to no clinically important difference)
(d) Unclear allocation concealment
(e) 2/2 unclear allocation concealment; 1/2 (26.2% weighted) unclear blinding and unclear baseline demographics
(f) Unclear allocation concealment and blinding; also, unclear baseline comparability as only includes those in each group who achieved remission; therefore, there are fewer participants in the vitamin D or vitamin D analogue group
(g) Surrogate outcome for duration of remission and definition of relapse = requiring re-treatment (not maintaining clear/nearly clear)
(h) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit in favour of vitamin D or vitamin D analogue to no clinically important difference)
(i) No SD given
(j) 7/7 unclear allocation concealment; 4/7 unclear blinding (55.5% weighted); 1/7 (22% weighted) unclear baseline demographics; 1/7 (11.2% weighted) dropout rate not stratified by group
(k) No statistically significant heterogeneity but one study (Bruce) favours a different treatment
(l) 3/3 unclear allocation concealment; 2/3 (81.8% weighted) unclear blinding
(m) No statistically significant heterogeneity but one study (Kragballe) favours a different treatment
(n) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(o) 2/2 unclear allocation concealment; 1/2 (58.4% weighted) unclear blinding and unclear baseline demographics

8.1.8.2 Evidence statements

In people with psoriasis, potent corticosteroid was statistically significantly better than vitamin D or vitamin D analogue for:

- Investigator's assessment (clear/nearly clear) at 4-8 weeks for calcipotriol once or twice daily or calcitriol twice daily compared to betamethasone dipropionate once or twice daily or betamethasone valerate twice daily [6 between-patient studies; 3136 participants; very low quality evidence][171,180,183,184,189,200]
- Patient's assessment (clear/nearly clear) at 4 weeks for calcipotriol once or twice daily compared to betamethasone dipropionate once or twice daily [2 between-patient studies; 1684 participants; low to moderate quality evidence][183,189]
- Withdrawals due to adverse events at 4-8 weeks for calcipotriol once or twice daily or calcitriol twice daily compared to betamethasone dipropionate once or twice daily, betamethasone valerate twice daily or fluocinonide twice daily [7 studies (6 between- and 1 within-patient); 3082 participants (3427 randomised units); low quality evidence][161,168,171,180,181,183,189]

In people with psoriasis, vitamin D or vitamin D analogue was statistically significantly better than potent corticosteroid for:

- Patient's assessment (clear/nearly clear) at 6 weeks for calcipotriol twice daily compared to betamethasone valerate twice daily [2 studies (1 between- and 1 within-patient); 743 participants (1085 randomised units); low quality evidence][168,181]
- % change in PASI at 6-8 weeks for calcipotriol twice daily compared to betamethasone valerate twice daily [2 studies (1 between- and 1 within-patient); 754 participants (1096 randomised units); moderate quality evidence][168,171]
- Relapse rate (requiring re-treatment [not maintaining clear/nearly clear] within 8-weeks post treatment) for calcitriol twice daily compared with betamethasone dipropionate twice daily [1 between-patient study; 131 participants; very low quality evidence][180]

In people with psoriasis, there was no statistically significant difference between potent corticosteroid and vitamin D or vitamin D analogue for:

- Withdrawals due to lack of efficacy at 6 weeks for calcipotriol or calcitriol twice daily compared with betamethasone dipropionate or valerate twice daily [3 studies (1 between- and 2 within-patient); 976 participants (1321 randomised units); very low quality evidence] [168,180,181]
- Skin atrophy at 4-8 weeks for calcipotriol twice daily vs betamethasone dipropionate or valerate twice daily [2 between-patient studies; 1038 participants; very low quality evidence][171,200]

Evidence statement for individual study where no statistical analysis could be performed

In people with psoriasis, vitamin D or vitamin D analogue was better than potent corticosteroid for:

- Mean time to relapse (requiring re-treatment [not maintaining clear/nearly clear] within 8-weeks post treatment) for calcitriol twice daily compared with betamethasone dipropionate twice daily [1 between-patient study; 131 participants; very low quality evidence][180]

8.1.8.3 Heterogeneity

- For the outcome of investigator's assessment of achieving clear/nearly clear status heterogeneity was present. The heterogeneity could not be explained by any of the pre-specified subgroups for investigation or by excluding studies at higher risk of bias.
- For the outcome of patient's assessment of achieving clear/nearly clear status heterogeneity was present. The heterogeneity was explained by creating subgroups based on treatment frequency and the specific agent, suggesting that betamethasone valerate may be less effective than betamethasone dipropionate.
- There was no significant heterogeneity for the remaining outcomes.

8.1.9 Concurrent vitamin D or vitamin D analogue and potent corticosteroid (one in the morning and one in the evening) vs. vitamin D or vitamin D analogue alone

8.1.9.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concurrent vitamin D or analogues and potent corticosteroid	Vitamin D or vitamin D analogue	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol and betamethasone valerate vs calcipotriol OD (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	94/174 (54%)	49/172 (28.5%)	RR 1.9 (1.44 to 2.49)	256 more per 1000 (from 125 more to 424 more)	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Calcipotriol and betamethasone valerate vs calcipotriol BD (follow-up 6-8 weeks)											
2 Kragballe 1998 Ruzicka 1998	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	serious[c]	None	154/252 (61.1%)	121/258 (46.9%)	RR 1.32 (1.12 to 1.54)	150 more per 1000 (from 56 more to 253 more)	⊕⊕OO LOW
Investigator's assessment (clear/nearly clear among those who did not respond to calcipotriol after 2 weeks) - Calcipotriol and betamethasone valerate vs calcipotriol BD (follow-up 6 weeks)											
1 Ruzicka 1998	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[c]	None	27/39 (69.2%)	22/49 (44.9%)	RR 1.54 (1.06 to 2.24)	242 more per 1000 (from 27 more to 557 more)	⊕⊕OO LOW

Patient's assessment (clear/nearly clear) - Calcipotriol and betamethasone valerate vs calcipotriol OD (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	89/174 (51.1%)	46/172 (26.7%)	RR 1.91 (1.44 to 2.55)	243 more per 1000 (from 118 more to 415 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) - Calcipotriol and betamethasone valerate vs calcipotriol BD (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	None	89/174 (51.1%)	69/172 (40.1%)	RR 1.28 (1.01 to 1.61)	112 more per 1000 (from 4 more to 245 more)	⊕⊕OO LOW
Withdrawals due to adverse events - Calcipotriol and betamethasone valerate vs calcipotriol OD (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	None	3/168 (1.8%)	8/163 (4.9%)	RR 0.36 (0.1 to 1.35)	31 fewer per 1000 (from 44 fewer to 17 more)	⊕OOO VERY LOW
Withdrawals due to adverse events - Calcipotriol and corticosteroid (betamethasone valerate or diflucortolone valerate) vs calcipotriol BD (follow-up 4-8 weeks)											
3 Kragballe 1998 Ruzicka 1998 Salmhofer 2000	randomised trials[f]	serious[g]	no serious inconsistency	no serious indirectness	very serious[e]	None	4/308 (1.3%)	8/303 (2.6%)	RR 0.52 (0.17 to 1.61)	13 fewer per 1000 (from 22 fewer to 16 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy - Calcipotriol and betamethasone valerate vs calcipotriol OD (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	None	1/166 (0.6%)	2/174 (1.1%)	RR 0.52 (0.05 to 5.73)	6 fewer per 1000 (from 11 fewer to 54 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy - Calcipotriol and betamethasone/diflucortolone valerate vs calcipotriol BD (follow-up 4-8 weeks)											
2 Kragballe 1998 Salmhofer 2000	randomised trials[f]	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	None	1/229 (0.44%)	3/223 (1.3%)	RR 0.32 (0.03 to 3.06)	9 fewer per 1000 (from 13 fewer to 28 more)	⊕OOO VERY LOW

(a) Unclear allocation concealment and blinding
(b) 2/2 unclear allocation concealment and blinding; 1/2 includes only patients with at least 4 weeks therapy, but this means just 2 weeks randomised
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit of concurrent treatment to no clinically important difference)
(d) Unclear allocation concealment and blinding; includes only patients with at least 4 weeks therapy, but this means just 2 weeks randomised
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(f) Data for Salmhofer are from a published Cochrane Review
(g) 3/3 unclear allocation concealment and blinding; 1/3 includes only patients with at least 4 weeks therapy, but this means just 2 weeks randomised

8.1.9.2 Evidence statements

In people with psoriasis, concurrent vitamin D or vitamin D analogue and potent corticosteroid treatment (one applied in the morning and one in the evening) was statistically significantly better than vitamin D or vitamin D analogue alone for:

- Investigator's assessment (clear/nearly clear)at 6-8 weeks for calcipotriol and betamethasone valerate compared with calcipotriol once or twice daily [2 between-patient studies; 682 participants; low to moderate quality evidence][190,202]
- Investigator's assessment (clear/nearly clear among those who did not respond to calcipotriol after 2 weeks) at 6 weeks for calcipotriol and betamethasone valerate compared with calcipotriol twice daily [1 between-patient study; 88 participants; low quality evidence][202]
- Patient's assessment (clear/nearly clear) at 8 weeks for calcipotriol and betamethasone valerate compared with calcipotriol once or twice daily [1 between-patient study; 518 participants; low to moderate quality evidence][190]

In people with psoriasis, there was no statistically significant difference between concurrent vitamin D or vitamin D analogue and potent corticosteroid treatment (one applied in the morning and one in the evening) and vitamin D or vitamin D analogue alone for:

- Withdrawals due to adverse events at 4-8 weeks for calcipotriol and betamethasone valerate or diflucortolone valerate compared with calcipotriol once or twice daily [3 studies (2 between- and 1 within-patient); 711 participants (774 randomised units); very low quality evidence][173,190,202]
- Withdrawals due to lack of efficacy calcipotriol and betamethasone valerate or diflucortolone valerate compared with calcipotriol once or twice daily [2 studies (1 between- and 1 within-patient); 563 participants (626 randomised units); very low quality evidence][173,190]

8.1.9.3 Heterogeneity

- For the outcomes of investigator's and patient's assessment of achieving clear/nearly clear status heterogeneity was present. The heterogeneity was removed by separating into subgroups based on frequency of administration of vitamin D or vitamin D analogue, suggesting that concurrent use of vitamin D or vitamin D analogue and potent steroid (one applied in the morning and one in the evening) is clinically more effective than once daily vitamin D or vitamin D analogue alone, but the effect in favour of the concurrent use is smaller compared with twice daily vitamin D or vitamin D analogue application.
- There was no significant heterogeneity for the remaining outcomes but OD and BD subgroups were kept separate where necessary to avoid double counting data from the Kragballe1998 study.

8.1.10 Combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate) vs. vitamin D or vitamin D analogue alone

8.1.10.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined product	Vitamin D or vitamin D analogue	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – Combination OD vs. vitamin D or vitamin D analogue (calcipotriol or tacalcitol) OD (follow-up 4-8 weeks)											
4 Fleming 2010A Kaufmann 2002 Langley 2011 A Ortonne 2004	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	536/1084 (49.4%)	192/995 (19.3%)	RR 2.65 (2.3 to 3.05)	318 more per 1000 (from 251 more to 396 more)	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Combination OD vs. vitamin D or vitamin D analogue (calcipotriol) BD (follow-up 4-8 weeks)											
2 Guenther 2002 Kragballe 2004	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	None	273/472 (57.8%)	248/554 (44.8%)	RR 1.31 (1.16 to 1.48)	139 more per 1000 (from 72 more to 215 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) - Combination OD vs. vitamin D or vitamin D analogue (calcipotriol or tacalcitol) OD or BD (follow-up 4-8 weeks)											
4 Kaufmann 2002 Guenther 2002 Langley 2011 A Ortonne 2004	randomised trials	serious[c]	very serious[d]	no serious indirectness	no serious imprecision	None	628/1060 (59.2%)	333/1122 (29.7%)	RR 2.05 (1.35 to 3.11)	312 more per 1000 (from 104 more to 626 more)	⊕OOO VERY LOW
% change in PASI – Combination OD vs. vitamin D or vitamin D analogue (calcipotriol or tacalcitol) OD or BD (follow-up 4-8 weeks; Better indicated by lower values)											
5 Fleming 2010A Kaufmann 2002	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	None	1037	1297	-	MD 11.62 lower (14.87 to 8.37 lower)	⊕⊕⊕O MODERATE

Kragballe 2004 Guenther 2002 Langley 2011 A											
Relapse rate at 8 weeks post-treatment - Combination OD vs. tacalcitol OD (follow-up 8 weeks + 8 weeks post-treatment)											
1 Langley 2011 A	randomised trials	very serious[f]	no serious inconsistency	serious[g]	serious[h]	None	28/67 (41.8%)	7/31 (22.6%)	RR 1.85 (0.91 to 3.77)	192 more per 1000 (from 20 fewer to 625 more)	⊕OOO VERY LOW
Median time to relapse – Combination OD vs. tacalcitol OD (follow-up 8 weeks + 8 weeks post-treatment)											
1 Langley 2011 A	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	serious[i]	None	67	31	-	Combination: 63 days Vitamin D: 61 days	⊕OOO VERY LOW
Withdrawals due to adverse events – Combination OD vs. vitamin D or vitamin D analogue (calcipotriol or tacalcitol) OD or BD (follow-up 4-8 weeks)											
3 Kaufmann 2002 Guenther 2002 Langley 2011 A	randomised trials	serious[j]	no serious inconsistency	no serious indirectness	no serious imprecision	None	6/797 (0.75%)	23/839 (2.7%)	RR 0.28 (0.12 to 0.67)	20 fewer per 1000 (from 9 fewer to 24 fewer)	⊕⊕⊕O MODERATE
Withdrawals due to lack of efficacy - Combination OD vs. calcipotriol BD (follow-up 4 weeks)											
1 Guenther 2002	randomised trials	serious[k]	no serious inconsistency	no serious indirectness	very serious[l]	None	0/151 (0%)	2/227 (0.9%)	RR 0.3 (0.01 to 6.21)	6 fewer per 1000 (from 9 fewer to 46 more)	⊕OOO VERY LOW
Skin atrophy - Combination OD vs. calcipotriol BD (follow-up 4-12 weeks)											
2 Kragballe 2004 Guenther 2002	randomised trials	serious[m]	no serious inconsistency	serious[n]	very serious[l]	None	2/473 (0.42%)	1/554 (0.18%)	RR 2.09 (0.27 to 16.53)	2 more per 1000 (from 1 fewer to 28 more)	⊕OOO VERY LOW

(a) 4/4 unclear allocation concealment; 1/4 single blind; 4/4 differential dropout (higher with vitamin D or vitamin D analogue, but acceptable level in all but 1 study)

(b) 2/2 unclear allocation concealment; 1/2 (59.1% weighted) double blind in combination arm but single blind (investigator) in vitamin D or vitamin D analogue group

(c) 4/4 unclear allocation concealment; 1/4 single blind (investigator); 3/4 differential dropout rate (but only >20% in one study)

(d) Heterogeneity was present (I^2 = 93%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect)

(e) 5/5 unclear allocation concealment; 1/5 (13.8% weighted) single blind (investigator); 1/5 (35.2% weighted) double blind in combination arm but single blind (investigator) in vitamin D or vitamin D analogue group; 3/5 differential dropout (but none >20%)

(f) Unclear allocation concealment and differential dropout rate (higher in vitamin D or vitamin D analogue group but not >20%); also, unclear baseline comparability as only includes those in each group who achieved remission; therefore, there are fewer participants in the vitamin D or vitamin D analogue alone group

(g) Surrogate outcome for duration of remission

(h) Confidence interval ranges from clinically significant effect to no effect

(i) No range given
(j) 3/3 unclear allocation concealment; 1/3 (17.7% weighted) single blind (investigator); 2/3 differential dropout rate (but not >20%)
(k) Unclear allocation concealment
(l) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(m) 2/2 unclear allocation concealment; 1/2 (38.3% weighted) double blind in combination arm but single blind (investigator) in vitamin D or vitamin D analogue group and differential dropout (but not >20%)
(n) Data are for full study period (so combination group received vitamin D or vitamin D analogue only for the final 4 of 12 weeks)

8.18.10.2 Evidence statements

In people with psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate once daily was statistically significantly better than calcipotriol once or twice daily or tacalcitol once daily for:

- Investigator's assessment (clear/nearly clear)at 4-8 weeks [6 between-patient studies; 1249 participants; moderate quality evidence][169,184,185,189,191,199]
- Patient's assessment (clear/nearly clear) at 4-8 weeks [4 between-patient studies; 2182 participants; very low quality evidence][169,185,189,199]
- Percentage change in PASI at 4-8 weeks [5 between-patient studies; 2334 participants; moderate quality evidence][169,184,185,189,191]
- Withdrawals due to adverse events at 4-8 weeks [3 between-patient studies; 1636 participants; moderate quality evidence][169,185,189]

In people with psoriasis, there was no statistically significant difference between a combined product containing calcipotriol monohydrate and betamethasone dipropionate once daily and vitamin D or vitamin D analogue once or twice daily for:

- Relapse rate at 8 weeks post-treatment for the combination product compared with tacalcitol once daily [1 between-patient study; 98 participants; very low quality evidence][169]
- Withdrawals due to lack of efficacy at 4 weeks for the combination product compared with calcipotriol twice daily [1 between-patient study; 378 participants; very low quality evidence][185]
- Skin atrophy at 4-12 weeks for the combination product compared with calcipotriol twice daily [2 between-patient studies; 1027 participants; very low quality evidence][185,191]

Evidence statement for individual study where no statistical analysis could be performed

In people with psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate once daily was better than vitamin D or vitamin D once daily for:

- Median time to relapse at 8 weeks post-treatment among those who had achieved remission with the combination product compared with tacalcitol once daily [1 between-patient study; 98 participants; very low quality evidence][169]

8.1.11 Heterogeneity

- For the outcome of investigator's assessment of achieving clear/nearly clear status heterogeneity was present. The heterogeneity was removed by separating into subgroups based on frequency of administration of vitamin D or vitamin D analogue, suggesting that use of combined vitamin D or vitamin D analogue and potent steroid is clinically more effective than once daily vitamin D or vitamin D analogue alone, but the effect in favour of the combined use was smaller compared with twice daily vitamin D or vitamin D analogue application.
- For the outcome of patient's assessment of achieving clear/nearly clear status high heterogeneity was present. The heterogeneity was not fully explained by any of the pre-specified subgroups although for the comparison with once daily vitamin D or vitamin D analogue the combination was clearly clinically more effective in all studies, but again the effect in favour of the combined use was smaller compared with twice daily vitamin D or vitamin D analogue application.
- There was no significant heterogeneity for the remaining outcomes.

8.1.12 Combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate) vs. potent corticosteroid

8.1.12.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and corticosteroid combination	Potent corticosteroid	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – combination OD vs betamethasone dipropionate OD (follow-up 4-8 weeks)											
2 Fleming 2010A Kaufmann 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	320/652 (49.1%)	190/559 (34%)	RR 1.53 (1.33 to 1.76)	180 more per 1000 (from 112 more to 258 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) – combination OD vs betamethasone dipropionate OD (follow-up 4 weeks)											
1 Kaufmann 2002	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	None	316/490 (64.5%)	216/476 (45.4%)	RR 1.42 (1.26 to 1.6)	191 more per 1000 (from 118 more to 272 more)	⊕⊕⊕O MODERATE

% change in PASI – combination OD vs betamethasone dipropionate OD (follow-up 4-8 weeks; Better indicated by lower values)											
2 Fleming 2010A Kaufmann 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	652	559	-	MD 9.94 lower (15.75 to 4.14 lower)	⊕⊕⊕O MODERATE
Withdrawals due to adverse events – combination OD vs betamethasone dipropionate OD (follow-up 4 weeks)											
1 Kaufmann 2002	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	very serious[c]	None	3/480 (0.63%)	5/452 (1.1%)	RR 0.56 (0.14 to 2.35)	5 fewer per 1000 (from 10 fewer to 15 more)	⊕OOO VERY LOW

(a) 2/2 unclear allocation concealment
(b) Unclear allocation concealment
(c) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.14 12.2 Evidence statements

In people with psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate was statistically significantly better than potent corticosteroid (betamethasone dipropionate once daily) for:

- Investigator's assessment (clear/nearly clear) at 4-8 weeks [2 between-patient studies; 1211 participants; moderate quality evidence][184,189]
- Patient's assessment (clear/nearly clear) at 4 weeks [1 between-patient study; 966 participants; moderate quality evidence][189]
- Percentage change in PASI at 4-8 weeks [2 between-patient studies; 1211 participants; moderate quality evidence] [184,189]

In people with psoriasis, there was no statistically significant difference between a combined product containing calcipotriol monohydrate and betamethasone dipropionate and potent corticosteroid (betamethasone dipropionate once daily)for:

- Withdrawals due to adverse events at 4 weeks [1 between-patient study; 932 participants; very low quality evidence][189]

8.13 12.3 Heterogeneity

- There was no significant heterogeneity for the any of the outcomes.

8.15 13 Combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate) then vitamin D or vitamin D analogue vs. vitamin D or vitamin D analogue alone

8.17 13.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and corticosteroid combination then vitamin D	Vitamin D	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – Combination (OD) (8 wk) then calcipotriol OD (4 wk) vs. calcipotriol BD (12 wk) (follow-up 12 weeks)											
1 Kragballe 2004	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	178/322 (55.3%)	133/327 (40.7%)	RR 1.36 (1.15 to 1.6)	146 more per 1000 (from 61 more to 244 more)	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Combination (OD) (4 wk) then calcipotriol OD weekdays/ combination weekends (8 wks) vs. calcipotriol BD (12 wk) (follow-up 12 weeks)											
1 Kragballe 2004	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	154/323 (47.7%)	133/327 (40.7%)	RR 1.17 (0.99 to 1.39)	69 more per 1000 (from 4 fewer to 159 more)	⊕⊕OO LOW
Investigator's assessment (clear/nearly clear) - Combination (OD) (4 wk) then calcipotriol OD (4 wks) vs. tacalcitol OD (8 wk) (follow-up 8 weeks)											
1 Ortonne 2004	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/249 (50.6%)	59/252 (23.4%)	RR 2.16 (1.68 to 2.79)	272 more per 1000 (from 159 more to 419 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) - Combination (OD) (4 wk) then calcipotriol OD (4 wks) vs. tacalcitol OD (8 wk) (follow-up 8 weeks)											
1 Ortonne 2004	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/249 (52.2%)	68/252 (27%)	RR 1.93 (1.53 to 2.45)	251 more per 1000 (from 143 more to 391 more)	⊕⊕⊕O MODERATE
% change in PASI - Combination (OD) (8 wk) then calcipotriol OD (4 wk) vs. calcipotriol BD (12 wk) (follow-up 12 weeks; Better indicated by lower values)											
1 Kragballe 2004	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	322	327	-	MD 9.2 lower (14.68 to 3.72 lower)	⊕⊕⊕O MODERATE
% change in PASI - Combination (OD) (4 wk) then vitamin D or vitamin D analogue OD weekdays/ combination OD weekends (8 wks) vs. calcipotriol BD (12 wk) (follow-up 12 weeks; Better indicated by lower values)											
1 Kragballe	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	323	327	-	MD 4.4 lower (8.35 to 0.45 lower)	⊕⊕⊕O MODERATE

2004											
% change in PASI - Combination (OD) (4 wk) then calcipotriol OD (4 wks) vs. tacalcitol OD (8 wk) (follow-up 8 weeks; Better indicated by lower values)											
1 Ortonne 2004	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	252	-	MD 20.6 lower (32.87 to 8.33 lower)	⊕⊕⊕O MODERATE
Withdrawal due to adverse events - Combination (OD) (4 wk) then calcipotriol BD (8 wk) vs calcipotriol BD (12 wk) (follow-up 12 weeks)											
1 Saraceno 2007	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	3/53 (5.7%)	2/48 (4.2%)	RR 1.36 (0.24 to 7.79)	15 more per 1000 (from 32 fewer to 283 more)	⊕OOO VERY LOW
Withdrawal due to adverse events - Combination (OD) (4 wk) then calcipotriol OD (4 wks) vs. tacalcitol OD (8 wk) (follow-up 8 weeks)											
1 Ortonne 2004	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[e]	none	6/223 (2.7%)	11/228 (4.8%)	RR 0.56 (0.21 to 1.48)	21 fewer per 1000 (from 38 fewer to 23 more)	⊕OOO VERY LOW
Withdrawal due to lack of efficacy - Combination (OD) (4 wk) then calcipotriol BD (8 wk) vs calcipotriol BD (12 wk) (follow-up 12 weeks)											
1 Saraceno 2007	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	1/51 (2%)	3/49 (6.1%)	RR 0.32 (0.03 to 2.98)	42 fewer per 1000 (from 59 fewer to 121 more)	⊕OOO VERY LOW
Withdrawal due to lack of efficacy - Combination (OD) (4 wk) then calcipotriol OD (4 wks) vs. tacalcitol OD (8 wk) (follow-up 8 weeks)											
1 Ortonne 2004	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[e]	none	3/220 (1.4%)	8/225 (3.6%)	RR 0.38 (0.1 to 1.43)	22 fewer per 1000 (from 32 fewer to 15 more)	⊕OOO VERY LOW
Skin atrophy - Combination (OD) (8 wk) then calcipotriol OD (4 wk) vs. calcipotriol BD (12 wk) (follow-up 12 weeks)											
1 Kragballe 2004	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	1/322 (0.31%)	0/327 (0%)	RR 3.05 (0.12 to 74.51)	-	⊕OOO VERY LOW
Skin atrophy - Combination (OD) (4 wk) then calcipotriol OD weekdays/ combination OD weekends (8 wks) vs. calcipotriol BD (12 wk) (follow-up 12 weeks)											
1 Kragballe 2004	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/322 (0%)	0/327 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE

(a) Unclear allocation concealment and calcipotriol group only single blind (investigator)

(b) Confidence interval ranges from clinically important effect to no effect

(c) Unclear allocation concealment and high differential dropout (15.7% in combination group and 20.2% in tacalcitol group)

(d) Unblinded and high dropout rate (33.3% in combination group and 38.7% in calcipotriol group)
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.13.2 Evidence statements

In people with psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate then vitamin D or vitamin D analogue was statistically significantly better than topical vitamin D or vitamin D analogue for:

- Investigator's assessment (clear/nearly clear) for a combined product once daily for 4 weeks then calcipotriol once daily for 4 weeks compared to tacalcitol once daily for 8 weeks; a combined product once daily for 8 weeks then calcipotriol once daily for 4 weeks vs. calcipotriol BD for 12 weeks [2 between-patient studies; 1150 participants; moderate quality evidence][191;199]
- Patient's assessment (clear/nearly clear) for a combined product once daily for 4 weeks then calcipotriol once daily for 4 weeks compared to tacalcitol once daily for 8 weeks [1 between-patient study; 501 participants; moderate quality evidence][199]
- Percentage change in PASI for a combined product once daily for 4 weeks then calcipotriol once daily weekdays/a combined product once daily at weekends for 8 weeks compared to calcipotriol twice daily for 12 weeks; a combined product once daily for 8 weeks then calcipotriol once daily for 4 weeks vs. calcipotriol twice daily for 12 weeks [1 between-patient study; 972 participants; moderate quality evidence][191]
- Percentage change in PASI for a combined product once daily for 4 weeks then calcipotriol once daily for 4 weeks compared to tacalcitol once daily for 8 weeks [1 between-patient study; 501 participants; moderate quality evidence][199]

In people with psoriasis, there were no events with either a combined product containing calcipotriol monohydrate and betamethasone dipropionate then vitamin D or vitamin D analogue or topical vitamin D or vitamin D analogue for:

- Skin atrophy for a combined product once daily for 4 weeks then calcipotriol once daily weekdays/ a combined product once daily at weekends for 8 weeks compared to calcipotriol twice daily for 12 weeks [1 between-patient study; 649 participants; moderate quality evidence][191]

In people with psoriasis, there was no statistically significant difference between a combined product containing calcipotriol monohydrate and betamethasone dipropionate then vitamin D or vitamin D analogue and topical vitamin D or vitamin D analogue for:

- Investigator's assessment (clear/nearly clear) for a combined product once daily for 4 weeks then calcipotriol once daily weekdays/a combined product once daily at weekends for 8 weeks compared to calcipotriol twice daily for 12 weeks [1 between-patient study; 650 participants; low quality evidence] [191]
- Withdrawal due to adverse events for a combined product once daily for 4 weeks then calcipotriol twice daily for 8 weeks compared to calcipotriol twice daily for 12 weeks [1 between-patient study; 101 participants; very low quality evidence][203]
- Withdrawal due to adverse events for a combined product once daily for 4 weeks then calcipotriol once daily for 4 weeks compared to tacalcitol once daily for 8 weeks [1 between-patient study; 451 participants; very low quality evidence][199]

- Withdrawal due to lack of efficacy for a combined product once daily for 4 weeks then calcipotriol twice daily for 8 weeks compared to calcipotriol twice daily for 12 weeks [1 between-patient study; 100 participants; very low quality evidence][203]
- Withdrawal due to lack of efficacy for a combined product once daily for 4 weeks then calcipotriol once daily for 4 weeks compared to tacalcitol once daily for 8 weeks [1 between-patient study; 445 participants; very low quality evidence][199]
- Skin atrophy for a combined product once daily for 8 weeks then calcipotriol once daily for 4 weeks compared to calcipotriol twice daily for 12 weeks [1 between-patient study; 649 participants; very low quality evidence][191]

8.17.3 Heterogeneity

- Not applicable as the studies assessed slightly different comparisons and so were not a combined

8.18 Combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate) vs. vitamin D or vitamin D analogue (52 weeks maintenance)

This study enrolled patients with plaque psoriasis of at least moderate severity and allowed treatment once daily according to the randomised intervention schedule for up to 52 weeks (52 weeks of the combination product vs 4 weeks of the combination product then 48 weeks with calcipotriol alone vs alternating 4-week periods of treatment with the combination product and calcipotriol alone); however, to accord with clinical practice, topical treatments were only applied when required.

8.18.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and corticosteroid combination	Vitamin D or vitamin D analogue	Relative (95% CI)	Absolute	
Investigator's assessment of treatment success (absent, very mild or mild disease) – Combination OD (52 wk) vs. combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	none	80/104 (76.9%)	62/89 (69.7%)	RR 1.1 (0.93 to 1.31)	70 more per 1000 (from 49 fewer to 216 more)	⊕OOO VERY LOW

Investigator's assessment of treatment success (absent, very mild or mild disease) – Combination OD (52 wk) vs. alternating combination OD and calcipotriol OD (52 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[d]	no serious inconsistency	serious[b]	no serious imprecision	none	80/104 (76.9%)	78/104 (75%)	RR 1.03 (0.88 to 1.2)	22 more per 1000 (from 90 fewer to 150 more)	⊕⊕OO LOW
Investigator's assessment of treatment success (absent, very mild or mild disease) - Alternating combination OD and calcipotriol OD (52 wk) vs combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[e]	no serious inconsistency	serious[b]	serious[c]	none	78/104 (75%)	62/89 (69.7%)	RR 1.08 (0.9 to 1.28)	56 more per 1000 (from 70 fewer to 195 more)	⊕OOO VERY LOW
Skin atrophy - Combination OD (52 wk) vs. combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[f]	none	4/212 (1.9%)	2/209 (0.96%)	RR 1.97 (0.37 to 10.65)	9 more per 1000 (from 6 fewer to 92 more)	⊕OOO VERY LOW
Skin atrophy - Combination OD (52 wk) vs. alternating combination OD and calcipotriol OD (52 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[f]	none	4/212 (1.9%)	1/213 (0.47%)	RR 4.02 (0.45 to 35.66)	14 more per 1000 (from 3 fewer to 163 more)	⊕OOO VERY LOW
Skin atrophy - Alternating combination OD and calcipotriol OD (52 wk) vs combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	very serious[f]	none	1/213 (0.47%)	2/209 (0.96%)	RR 0.49 (0.04 to 5.37)	5 fewer per 1000 (from 9 fewer to 42 more)	⊕OOO VERY LOW
Withdrawal due to adverse events – Combination OD (52 wk) vs. combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[f]	none	14/162 (8.6%)	16/155 (10.3%)	RR 0.84 (0.42 to 1.66)	17 fewer per 1000 (from 60 fewer to 68 more)	⊕OOO VERY LOW
Withdrawal due to adverse events - Combination OD (52 wk) vs. alternating combination OD and calcipotriol OD (52 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[f]	none	14/162 (8.6%)	11/168 (6.5%)	RR 1.32 (0.62 to 2.82)	21 more per 1000 (from 25 fewer to 119	⊕OOO VERY LOW

										more)	
Withdrawal due to adverse events - Alternating combination OD and calcipotriol OD (52 wk) vs combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	very serious[f]	none	11/168 (6.5%)	16/155 (10.3%)	RR 0.63 (0.3 to 1.32)	38 fewer per 1000 (from 72 fewer to 33 more)	⊕OOO VERY LOW
Withdrawal due to lack of efficacy - Combination OD (52 wk) vs. combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	35/183 (19.1%)	42/181 (23.2%)	RR 0.82 (0.55 to 1.23)	42 fewer per 1000 (from 104 fewer to 53 more)	⊕⊕OO LOW
Withdrawal due to lack of efficacy - Combination OD (52 wk) vs. alternating combination OD and calcipotriol OD (52 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[f]	none	35/183 (19.1%)	31/188 (16.5%)	RR 1.16 (0.75 to 1.8)	26 more per 1000 (from 41 fewer to 132 more)	⊕OOO VERY LOW
Withdrawal due to lack of efficacy - Alternating combination OD and calcipotriol OD (52 wk) vs combination OD (4 wk) then calcipotriol OD (48 wk) (follow-up 52 weeks)											
1 Kragballe 2006 (and 2006A)	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	serious[c]	none	31/188 (16.5%)	42/181 (23.2%)	RR 0.71 (0.47 to 1.08)	67 fewer per 1000 (from 123 fewer to 19 more)	⊕⊕OO LOW

(a) Unclear allocation concealment and blinding; high dropout rate (30% in combination group and 33.5% in calcipotriol group)
(b) Definition of success is too broad
(c) Confidence interval ranges from clinically important effect to no effect
(d) Unclear allocation concealment and blinding; high dropout rate (30% in combination group and 26.3% in alternating group)
(e) Unclear allocation concealment and blinding; high dropout rate (26.3% in alternating group and 33.5% in vitamin D or vitamin D analogue group)
(f) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.1714.2 Evidence statements

In people with psoriasis, there was no statistically significant difference between the maintenance regimens for 52 weeks maintenance for:

- Investigator's assessment of treatment success (absent, very mild or mild disease) at 52 weeks [1 between-patient study; 297 participants; low to very low quality evidence][192]
- Skin atrophy at 52 weeks [1 between-patient study; 634 participants; very low quality evidence][193]
- Withdrawal due to adverse events at 52 weeks [1 between-patient study; 485 participants; very low quality evidence][192,193]
- Withdrawal due to lack of efficacy at 52 weeks [1 between-patient study; 552 participants; low to very low quality evidence][192,193]

8.11.14.3 Heterogeneity

- Not applicable as this study assessed multiple comparisons and combining all results would lead to double counting of data.

8.11.15 Vitamin D or vitamin D analogue vs. dithranol

8.11.15.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or analogue	Dithranol	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol BD vs. dithranol OD (follow-up 8-12 weeks)											
3 Berth Jones 1992 Christensen 1999 Wall 1998	randomised trials	serious[a]	serious[b]	no serious indirectness[c]	serious[d]	none	278/473 (58.8%)	187/435 (43%)	RR 1.36 (1.10 to 1.68)	155 more per 1000 (from 43 more to 292 more)	⊕OOO VERY LOW
Investigator's assessment (clear/nearly clear) - Calcitriol BD vs. dithranol OD (follow-up 8 weeks)											
1 Hutchinson 2000	randomised trials	serious[e]	no serious inconsistency	serious[f]	very serious[g]	none	4/60 (6.7%)	9/54 (16.7%)	RR 0.4 (0.13 to 1.22)	100 fewer per 1000 (from 145 fewer to 37 more)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) - Calcipotriol BD vs. dithranol OD (follow-up 8-12 weeks)											
2 Berth Jones 1992 Wall 1998	randomised trials	serious[h]	no serious inconsistency	no serious indirectness	no serious imprecision	none	273/384 (71.1%)	188/358 (52.5%)	RR 1.36 (1.21 to 1.53)	189 more per 1000 (from 110 more to 278 more)	⊕⊕⊕O MODERATE
% change in PASI - Calcipotriol BD vs. dithranol OD (follow-up 8 weeks; Better indicated by lower values)											
1 van der Kerkhof 2006	randomised trials	serious[i]	no serious inconsistency	no serious indirectness	serious[j]	none	46	40	-	MD 6.6 higher (7.04 lower to 20.24 higher)	⊕⊕OO LOW

Withdrawals due to adverse events - Calcipotriol or calcitriol BD vs. dithranol OD (follow-up 8-12 weeks)											
5 Berth Jones 1992 Christensen 1999 Hutchinson 2000 van der Kerkhof 2006 Wall 1998	randomised trials	serious[k]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/561 (3.9%)	43/524 (8.2%)	RR 0.49 (0.3 to 0.79)	42 fewer per 1000 (from 17 fewer to 57 fewer)	⊕⊕⊕O MODERATE
Withdrawals due to lack of efficacy - Calcipotriol BD vs. dithranol OD (follow-up 8 weeks)											
1 van der Kerkhof 2006	randomised trials	serious[i]	no serious inconsistency	no serious indirectness	serious[j]	none	7/47 (14.9%)	4/49 (8.2%)	RR 1.82 (0.57 to 5.83)	67 more per 1000 (from 35 fewer to 394 more)	⊕⊕OO LOW
Relapse rate - Calcipotriol BD vs. dithranol OD (8 week post-treatment)											
1 Christensen 1999	randomised trials	very serious[l]	no serious inconsistency	serious[m]	serious[n]	none	50/62 (80.6%)	19/33 (57.6%)	RR 1.40 (1.02 to 1.92)	230 more per 1000 (from 12 more to 530 more)	⊕OOO VERY LOW
Median time to relapse - Calcipotriol BD vs. dithranol OD (follow-up 8 week post-treatment)											
1 Christensen 1999	randomised trials	very serious[l]	no serious inconsistency	no serious indirectness	very serious[o]	none	62	33	-	Calcipotriol: 29 days Dithranol: 56 days	⊕OOO VERY LOW

(a) 3/3 unclear allocation concealment; 2/3 open and 1/3 unclear blinding

(b) Heterogeneity was present (I^2 = 50%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect)

(c) 1/3 (2% weighted has strict definition of response - complete clearance)

(d) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit in favour of vitamin D or vitamin D analogue to no clinically important difference)

(e) Unclear allocation concealment and unblinded; high differential dropout rate (20% vitamin D or vitamin D analogue and 29.6% dithranol)

(f) Strict definition of response (complete clearance)

(g) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

(h) 2/2 unclear allocation concealment and unblended

(i) Unclear blinding and high differential dropout rate (vitamin D or vitamin D analogue 25.9%; dithranol 13.5%)

(j) Confidence interval ranges from clinically significant effect to no effect (default MID = 0.5 x median control group SD = 14.55%)

(k) 4/5 unclear allocation concealment; 3/5 unblinded and 2/5 unclear blinding; 2/5 (15.5% weighted) high differential dropout rate (one with more dropouts in vitamin D or vitamin D analogue group and one with more in dithranol group)

(l) Unclear allocation concealment and blinding; high dropout rate during post-treatment phase (full details not given but appears higher in dithranol group); only includes those who were at least 50% improved and willing to continue; therefore, unclear baseline comparability and fewer in the dithranol group

(m) Surrogate outcome for duration of remission

(n) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit in favour of dithranol to no clinically important difference)
(o) Interpreted from graphical representation

8.13.2 Evidence statements

In people with psoriasis, vitamin D or vitamin D analogue was statistically significantly better than dithranol for:

- Investigator's assessment (clear/nearly clear) at 8-12 weeks for calcipotriol twice daily compared to dithranol once daily [3 between-patient studies; 908 participants; very low quality evidence][159,162,207]
- Patient's assessment (clear/nearly clear) at 8-12 weeks for calcipotriol twice daily compared to dithranol once daily [2 between-patient studies; 742 participants; moderate quality evidence][159,207]
- Withdrawals due to adverse events at 8-12 weeks for calcipotriol or calcitriol twice daily compared to dithranol once daily [5 between-patient studies; 1085 participants; moderate quality evidence] [159,162,177,186,207]

In people with psoriasis, dithranol was statistically significantly better than vitamin D or vitamin D analogue for:

- Relapse rate at 8 weeks post treatment for calcipotriol twice daily compared to dithranol once daily [1 between-patient study; 95 participants; very low quality evidence][162]

In people with psoriasis, there was no statistically significant difference between dithranol and vitamin D or vitamin D analogue for:

- Investigator's assessment (clear/nearly clear) at 8 weeks for calcitriol twice daily compared to dithranol once daily [1 between-patient study; 114 participants; very low quality evidence][186]
- Percentage change in PASI at 8 weeks for calcipotriol twice daily compared to dithranol once daily [1 between-patient study; 86 participants; low quality evidence][177]
- Withdrawals due to lack of efficacy at 8 weeks for calcipotriol twice daily compared to dithranol once daily [1 between-patient study; 96 participants; low quality evidence] [177]

Evidence statement for individual study where no statistical analysis could be performed

In people with psoriasis, dithranol was better than vitamin D or vitamin D analogue for:

- Median time to relapse for a maximum follow-up of at 8 weeks post-treatment among those who had achieved remission with calcipotriol twice daily compared to dithranol once daily [1 between-patient study; 95 participants; very low quality evidence][162]

8.1.15.3 Heterogeneity

- For the outcome of investigator's assessment of achieving clear/nearly clear status heterogeneity was present. The heterogeneity was greatly reduced by separating into subgroups based on the specific vitamin D or vitamin D analogue used; suggesting that calcitriol may be less effective than dithranol but calcipotriol may be more effective. However, there was still some heterogeneity among the studies using calcipotriol, although all showed the same direction of effect.
- There was no significant heterogeneity for the remaining outcomes.

8.1.16 Vitamin D or vitamin D analogue vs. coal tar

8.1.16.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogue	Coal tar	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol BD vs 15% coal tar solution in aqueous cream OD (follow-up 6 weeks)											
1 Tham 1994	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/27 (48.1%)	3/27 (11.1%)	RR 4.33 (1.39 to 13.5)	370 more per 1000 (from 43 more to 1000 more)	⊕⊕⊕O MODERATE
Investigator's assessment (clear/nearly clear) - Calcipotriol BD vs. coal tar polytherapy (coal tar 5%/allantoin 2%/hydrocortisone cream 0.5%) BD (follow-up 8 weeks)											
1 Pinheiro 1997	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	serious[c]	none	47/65 (72.3%)	28/57 (49.1%)	RR 1.47 (1.09 to 1.99)	231 more per 1000 (from 44 more to 486 more)	⊕⊕OO LOW
Investigator's assessment (clear/nearly clear) - Calcipotriol BD vs. coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) BD (follow-up 12 weeks)											
1 Alora-Palli 2010	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	6/28 (21.4%)	14/27 (51.9%)	RR 0.41 (0.19 to 0.92)	306 fewer per 1000 (from 41 fewer to 420 fewer)	⊕OOO VERY LOW
% change in PASI - Calcipotriol BD vs 15% coal tar solution in aqueous cream OD (follow-up 6 weeks; Better indicated by lower values)											
1 Tham 1994	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27	27	-	MD 38.9 lower (50.95 to 26.85 lower)	⊕⊕⊕O MODERATE
% change in PASI - Calcipotriol BD vs. coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) BD (follow-up 12 weeks; Better indicated by lower values)											

1 Alora-Palli 2010	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	27	-	MD 21.7 higher (4.2 to 39.2 higher)	⊕⊕OO LOW
Relapse rate (6 weeks post-treatment) - Calcipotriol BD vs. coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) BD											
1 Alora-Palli 2010	randomised trials	very serious[f]	no serious inconsistency	serious[g]	no serious imprecision	none	7/9 (77.8%)	4/16 (25%)	RR 3.11 (1.24 to 7.79)	527 more per 1000 (from 85 more to 1000 more)	⊕OOO VERY LOW
Withdrawals due to adverse events - Calcipotriol BD vs 15% coal tar solution in aqueous cream OD (follow-up 6 weeks)											
1 Tham 1994	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[h]	none	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	-	⊕OOO VERY LOW
Withdrawals due to adverse events - Calcipotriol BD vs. coal tar polytherapy (coal tar 5%/allantoin 2%/hydrocortisone cream 0.5%) BD (follow-up 8 weeks)											
1 Pinheiro 1997	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	very serious[h]	none	1/62 (1.6%)	3/54 (5.6%)	RR 0.29 (0.03 to 2.71)	39 fewer per 1000 (from 54 fewer to 95 more)	⊕OOO VERY LOW
Withdrawals due to adverse events - Calcipotriol BD vs. coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) BD (follow-up 12 weeks)											
1 Alora-Palli 2010	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	0/27 (0%)	not pooled	not pooled	⊕⊕OO LOW

(a) Unclear allocation concealment and blinding
(b) Unclear allocation concealment and unblended
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit of vitamin D or vitamin D analogues to no clinically important difference)
(d) Unclear allocation concealment, single blind (investigator) and high differential dropout rate (16.7% in tar and 26.7% in calcipotriol group during treatment phase)
(e) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit of coal tar to no clinically important difference)
(f) Unclear allocation concealment, single blind (investigator) and high differential dropout rate (16.7% in tar and 26.7% in calcipotriol group during treatment phase); also only include those who achieved a PASI50; therefore, unclear baseline comparability and fewer in the calcipotriol group
(g) Surrogate outcome for duration of remission
(h) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.1.17 Evidence statements

In people with psoriasis, vitamin D or vitamin D analogue treatment was statistically significantly better than coal tar for:

- Investigator's assessment (clear/nearly clear) at 6-8 weeks for calcipotriol twice daily compared to 15% coal tar solution in aqueous cream once daily; calcipotriol twice daily compared to coal tar polytherapy (coal tar 5%/allantoin 2%/hydrocortisone cream 0.5%) twice daily [2 studies (1 within- and 1 between-patient); 149 participants (176 randomised units); low to moderate quality evidence][172,205]
- Percentage change in PASI at 6 weeks for calcipotriol twice daily compared to 15% coal tar solution in aqueous cream once daily [1 within-patient study; 27participants (54 randomised units); moderate quality evidence][205]

In people with psoriasis, coal tar was statistically significantly better than vitamin D or vitamin D analogue for:

- Investigator's assessment (clear/nearly clear) at 12 weeks for calcipotriol twice daily compared to coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) twice daily [1 between-patient study; 55 participants; very low quality evidence][157]
- Percentage change in PASI at 12 weeks for calcipotriol twice daily compared to coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) twice daily [1 between-patient study; 55 participants; low quality evidence][157]
- Relapse rate at 6 weeks post-treatment for calcipotriol twice daily compared to coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) twice daily [1 between-patient study; 25 participants; very low quality evidence][157]

In people with psoriasis, there were no events with either vitamin D or vitamin D analogue or coal tar for:

- Withdrawals due to adverse events at 12 weeks for calcipotriol twice daily compared to coal tar solution (liquor carbonis distillate (LCD 15%, equivalent to 2.3% coal tar) twice daily [1 between-patient study; 55 participants; low quality evidence][157]

In people with psoriasis, there was no statistically significant difference between vitamin D or vitamin D analogue and coal tar for:

- Withdrawals due to adverse events at 6 weeks for calcipotriol twice daily compared to 15% coal tar solution in aqueous cream once daily [1 within-patient study; 25 participants (50 randomised units); very low quality evidence][205]
- Withdrawals due to adverse events at 8 weeks for calcipotriol twice daily compared to coal tar polytherapy (coal tar 5%/allantoin 2%/hydrocortisone cream 0.5%) twice daily [1 between-patient study; 116 participants; very low quality evidence][172]

8.1617.1 Heterogeneity

- Heterogeneity was present for all outcomes. The heterogeneity was removed by separating into subgroups based on treatment duration. However, it is also possible that the coal tar formulation caused the heterogeneity, although this was thought to be clinically less likely to be the source of the inconsistency.

8.1.18 Vitamin D or vitamin D analogue once daily compared to vitamin D or vitamin D twice daily

8.2118.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Vitamin D	Vitamin D	Relative	Absolute	

		bias				considerations	OD	BD	(95% CI)		
Investigator's assessment (clear/nearly clear) – calcipotriol (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	49/172 (28.5%)	69/172 (40.1%)	RR 0.71 (0.53 to 0.96)	116 fewer per 1000 (from 16 fewer to 189 fewer)	⊕⊕OO LOW
Patient's assessment (clear/nearly clear) – calcipotriol (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	None	46/172 (26.7%)	69/172 (40.1%)	RR 0.67 (0.49 to 0.91)	132 fewer per 1000 (from 36 fewer to 205 fewer)	⊕⊕OO LOW
Withdrawals due to adverse events – calcipotriol (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	None	8/174 (4.6%)	6/174 (3.4%)	RR 1.33 (0.47 to 3.76)	11 more per 1000 (from 18 fewer to 95 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy – calcipotriol (follow-up 8 weeks)											
1 Kragballe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	None	2/174 (1.1%)	3/174 (1.7%)	RR 0.67 (0.11 to 3.94)	6 fewer per 1000 (from 15 fewer to 51 more)	⊕OOO VERY LOW

(a) Unclear allocation concealment and blinding
(b) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit in favour of twice daily application to no clinically important difference)
(c) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.14.2 Evidence statements

In people with psoriasis, calcipotriol twice daily was statistically significantly better than calcipotriol once daily for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [1 within-patient study; 344 participants; low quality evidence][190]
- Patient's assessment (clear/nearly clear) at 8 weeks [1 within-patient study; 344 participants; low quality evidence][190]

In people with psoriasis, there was no statistically significant difference between calcipotriol once daily and calcipotriol twice daily for:

- Withdrawal due to adverse events at 8 weeks [1 within-patient study; 348 participants; very low quality evidence][190]
- Withdrawal due to lack of efficacy at 8 weeks [1 within-patient study; 348 participants; very low quality evidence][190]

8.14.3 Heterogeneity

- Not applicable as only one study was available for this comparison

8.2 Time to remission / maximum effect (trunk and limbs)

8.2.1 Vitamin D or vitamin D analogues

8.2.1.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogue		
Time-to-remission (marked improvement or clearance (follow-up 1-8 weeks)									
1 Highton 1995	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol BD 124	Patients achieving marked improvement or clearance Week 1 9.6% Week 2 27.8% Week 4 54.2% Week 6 65.1% Week 8/EOT 69.8%	⊕⊕OO LOW
Time-to-remission (clear/nearly clear; follow-up 4-8 weeks)									
1 Fleming2010A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol OD 79	**Clear/nearly clear (investigator's static assessment)** Week 4 26 (16.0%) Week 8 44 (27.2%)	⊕⊕OO LOW
Time-to-remission (clear/nearly clear; follow-up 4-8 weeks)									

1 Langley 2011A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Tacalcitol OD 184	**Clear/nearly clear (investigator's static assessment)** Week 4 12 (6.5%) Week 8 33 (17.9%) **Clear/nearly clear (patient's static assessment)** Week 4 21/175 (12.0%) Week 8 35/163 (21.5%)	⊕⊕OO LOW
Time-to-maximum response (change in PASI; follow-up 2-6 weeks)									
1 Cunliffe 1992	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol BD 201	Mean (SD) change in PASI from baseline (mean at baseline = 8.67) Week 2 3.19 (3.61) Week 4 4.37 (4.70) Week 6 5.5 (9.54)	⊕⊕OO LOW
Time-to-maximum response (change in PASI; follow-up 2-4 weeks)									
1 Dubertret 1992	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol BD 65	Mean (SD) PASI during initial 4-week randomised treatment phase **Mean baseline PASI (n=65)** 14.2 ± 7.5 **After 2 weeks (n=62)** *Mean PASI* *8.6 ± 7.5* % change from baseline 41.2 ± 25.7 **After 4 weeks (n=60)** *Mean PASI* *6.3 ± 6.5* % change from baseline 58.6 ± 31.7	⊕⊕OO LOW

Time-to-maximum response (change in PASI; follow-up 2-12 weeks)									
1 Saraceno 2007	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol BD 75	**Mean PASI (SD)** Baseline 9.11 (4.09) 2 weeks 5.47 (3.47) 4 weeks 4.07 (3.33) 8 weeks 3.45 (3.77) 12 weeks 3.04 (3.76)	⊕⊕OO LOW
Time-to-maximum response (% change in PASI; follow-up 2-4 weeks)									
1 Ortonne 2004	observational studies[a]	no serious risk of bias[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Tacalcitol OD 252	**Mean % reduction in PASI score from baseline** 2 weeks 24.5% 4 weeks 33.3%	⊕⊕OO LOW
Time-to-maximum response (% change in PASI; follow-up 4-8 weeks)									
1 Langley 2011A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Tacalcitol OD 184	**% change in PASI** week 4 -37.3 week 8 -41.9	⊕⊕OO LOW
Time-to-maximum response (% change in mPASI [0.64.8]; follow-up 4-12 weeks)									
1 Alora-Palli 2010	observational studies[a]	no serious risk of bias[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol BD 28	**% change in PASI from baseline** Baseline 7.07 4 weeks 5.09 (-30.2%) 8 weeks 4.71 (-34.2%)	⊕⊕OO LOW

								12 weeks 4.66 (-36.5%)	
Time-to-maximum response (% change in PASI; follow-up 2-6 weeks)									
1 Tham 1994	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Calcipotriol BD 27	**Mean PASI (italics) and % change in PASI score from baseline** **Baseline** *6.6±4.9* **2 weeks** *4.1±3.4* -36.9±25.0% **4 weeks** *2.8±2.2* -57.5±19.4% **6 weeks** *2.0±2.1* -69.8±20.4%	⊕⊕OO LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm
(b) Unclear allocation concealment may have biased patient selection for this intervention
(c) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (38.7%)
(d) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (20.2%)
(e) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (26.7%)

8.2.1.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for vitamin D or vitamin D analogues (no statistical analysis could be performed).

In people with psoriasis, the time to remission when using vitamin D or vitamin D analogues varied between studies:

- Proportion achieving remission by 8 weeks ranged from 11.4 to 69.8% [3 studies; 387 participants; low quality evidence][166,169,184]
- The continued increase in responders between 4 and 8 weeks ranged from 7.6-15.6% [3 studies; 387 participants; low quality evidence][166,169,184]
- The continued increase in responders between 6 and 8 weeks was 4.7% [1 study; 124 participants; low quality evidence][166]
- Of those who achieved remission by the end of the trial at 8 weeks, 33.3-77.7% had responded by week 4 and 93.3% by week 6 on calcipotriol; but just 36.4% of those who achieved remission by the end of the trial had responded by week 4 on tacalcitol [3 studies; 387 participants; low quality evidence][166,169,184]

- The decrease in PASI from 2-4 weeks ranged from 1.18-2.4 points [4 studies; 368 participants; low quality evidence][163,181,203,205]
- The continued decrease in PASI from 4-6 weeks ranged from 0.8-1.13 points [2 studies; 228 participants; low quality evidence][181,205]
- The continued decrease in PASI from 8-12 weeks ranged from 0.05-0.41 points [2 studies; 103 participants; low quality evidence][157,203]
- The % decrease in PASI from 2-4 weeks ranged from 8.8-20.6% [5 studies; 620 participants; low quality evidence][163,181,199,203,205]
- The % decrease in PASI from 4 to 6 or 8 weeks ranged from 4.0-13.0% and from 8-12 weeks from 2.3-4.5% [5 studies; 515 participants; low quality evidence][157,169,181,203,205]
- The % decrease in PASI from 8-12 weeks ranged from 0.7-4.5% [2 studies; 103 participants; low quality evidence][157,203]

Summary

The evidence suggests that maximum response is not achieved in all patients by 8-12 weeks, with the response rate still increasing slightly at this time point, although the most rapid improvement was seen over the first 2-4 weeks, particularly for twice daily application.

8.2.2 Potent corticosteroids

8.2.2.1 Evidence profiles

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Potent corticosteroid		
Time-to- clearance or near clearance (follow-up 4-8 weeks)									
1 Fleming2010A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Betamethasone dipropionate OD 83	**Clear/nearly clear (investigator's static assessment)** Week 4 8 (9.6%) Week 8 14 (16.9%)	⊕⊕OO LOW
Time-to-marked improvement or clearance (follow-up 8-22 days)									
1	observational	no serious risk	no serious	no serious	no serious	none	Mometasone	Patients achieving marked improvement or	⊕⊕OO

Medansky 1987	studies[a]	of bias[b]	inconsistency	indirectness	imprecision		furoate OD 58	clearance 8 days 4/58 (6.9%) 15 days 12/55 (21.8%) 22 days 18/50 (36.0%)	LOW
Time-to-excellent or good improvement (follow-up 7-21 days)									
1 Sears 1997	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	serious indirectness[d]	no serious imprecision	none	Hydrocortisone buteprate BD 84	Patients achieving excellent or good improvement Day 7: 15/84 (17.9%) Day 14: 24/84 (28.2%) Day 21: 32/78 (41.3%)	⊕OOO VERY LOW
Mean time to remission (IAGI – clear, excellent or good) (follow-up 4 weeks)									
1 Olsen 1996 – study A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	no serious imprecision	serious[e]	Fluticasone propionate BD 88	**Investigator's assessment** **Week 1** Clear 0 Excellent/good 55% **Week 2** Clear 4% Excellent/good 60% **Week 3** Clear 4% Excellent/good 65% **Week 4** Clear 11% Excellent/good 60%	⊕OOO VERY LOW
Mean time to remission (IAGI – clear, excellent or good) (follow-up 4 weeks)									
1 Olsen 1996 – study B	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	no serious imprecision	serious[e]	Fluticasone propionate BD 105	**Investigator's assessment** **Week 1** Clear 0 Excellent/good 29% **Week 2**	⊕OOO VERY LOW

								Clear 0 Excellent/good 50% **Week 3** Clear 0 Excellent/good 65% **Week 4** Clear 3% Excellent/good 66%	
Time-to-maximum response (% change in PASI; follow-up 2-6 weeks)									
1 Thawornchaisit 2007	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Betamethasone valerate BD 30	Mean PASI and % change in PASI score from baseline **2 weeks** 12.95±3.4 -27.23±10.6% **4 weeks** 8.68±3.8 -51.41±18.2% **6 weeks** 5.52±4.5 -69.36±23.3%	⊕⊕OO LOW
Time-to-maximum response (change in PASI; follow-up 2-6 weeks)									
1 Cunliffe 1992	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Betamethasone valerate BD 200	**Mean (SD) change in PASI from baseline** Mean at baseline 9.35 2 weeks 3.39 (2.16) 4 weeks 4.50 (5.33) 6 weeks 5.32 (6.06)	⊕⊕OO LOW

1 *(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the*
2 *comparator arm*
3 *(b) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (21.5%)*
4 *(c) Unclear allocation concealment may have biased patient selection for this intervention*
5 *(d) Incorrect definition of response*
6 *(e) Note that only percentages of responders are available and it is unclear whether the same number of participants were assessed at each time point*

8.2.2.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for potent corticosteroids (no statistical analysis could be performed).

In people with psoriasis, the time to remission when using potent corticosteroids varied between studies:

- Proportion achieving remission by 3 weeks ranged from 36.0-41.3% on mometasone furoate or hydrocortisone buteprate [2 studies; 142 participants; low to very low quality evidence][170,174]
- Proportion achieving remission by 4 weeks on fluticasone propionate ranged from 69-71% [2 studies; 793 participants; very low quality evidence][211]
- Proportion achieving remission by 8 weeks on betamethasone dipropionate was 16.9% [1 study; 83 participants; low quality evidence][184]
- The continued increase in responders on mometasone furoate or hydrocortisone buteprate between 2 and 3 weeks ranged from 13.1-14.2%, meaning that 66.7 to 75.0% of those who responded during the trial had achieved remission by 2 weeks [2 studies; 142 participants; low to very low quality evidence][170,174]
- The continued increase in responders between 4-8 weeks of treatment on betamethasone dipropionate, was 7.3% [1 study; 83 participants; low quality evidence][184]
- The continued increase in responders between 3-4 weeks of treatment on fluticasone propionate, ranged from 2-4% [2 studies; 193 participants; very low quality evidence] [211]
- Of those who achieved remission by the end of the trial at 3 weeks, 66.7 to 75.0% had responded by week 2 on mometasone furoate or hydrocortisone buteprate [2 studies; 142 participants; low to very low quality evidence][170,174]
- Of those who achieved remission by the end of the trial at 4 weeks, 72.5-83.1% had responded by week 2 and 89.6-94.2% by week 3 on fluticasone propionate [2 studies; 193 participants; very low quality evidence][211]
- Of those who achieved remission by the end of the trial at 8 weeks on betamethasone dipropionate, 57.1% had responded by week 4 [1 study; 83 participants; low quality evidence][184]
- The continued decrease in PASI on betamethasone valerate from 4-6 weeks ranged from 0.82-3.16 points/8.8-17.95% [2 studies; 230 participants; low quality evidence][181,206]

Summary

The evidence suggests that maximum response is not achieved in all patients by 6-8 weeks, with the response rate still increasing slightly at this time point, although the most rapid improvement was seen over the first 2-4 weeks, particularly for twice daily application.

8.2.3 Very potent corticosteroids

8.2.3.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Very potent corticosteroid		
Mean time to maximum response (global severity score) (follow-up 4 weeks)									
1 Decroix 2004	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	Clobetasol propionate OD 189	Mean global severity score over time shows that maximum effect is not achieved by week 4 (gradual improvement still apparent)	⊕OOO VERY LOW
Mean time to maximum response (TSS) (follow-up 4 weeks)									
1 Lowe 2005	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	very serious[c]	none	Clobetasol propionate BD 162	Mean % change in TSS over time shows that maximum effect is not achieved by week 4	⊕OOO VERY LOW
Mean time to maximum response (TSS) (follow-up 4 weeks)									
1 Beutner 2006	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	very serious[c]	none	Clobetasol propionate BD 25	Mean TSS over time shows that maximum effect is not achieved by week 4 (gradual improvement still apparent)	⊕OOO VERY LOW
Mean time to maximum response (TSS) (follow-up 2 weeks)									
1 Lebwohl 2002	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	very serious[c]	none	Clobetasol propionate BD 61	Mean TSS over time shows that maximum effect is not achieved by week 2	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm
(b) Unclear allocation concealment may have biased patient selection for this intervention
(c) Interpreted from graphical representation
(d) Incorrect outcome measure

8.2.3.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for very potent corticosteroids (no statistical analysis could be performed).

In people with psoriasis, the time to remission or maximum response when using very potent corticosteroids varied between studies:

- Mean change in global severity score showed that a maximum effect was not reached by week 4 [4 studies; 437 participants; very low quality evidence][160,182,196,197]
- Mean change (or % change) in TSS showed that a maximum effect was not reached by week 2 or 4 [4 studies; 437 participants; very low quality evidence][160,182,196,197]

Summary

The evidence suggests that maximum response is not achieved in all patients by 2 or 4 weeks, with the response rate still increasing slightly at this time point. However, the most rapid effect is seen over the first 2 weeks.

8.2.4 Combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate)

8.2.4.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination		
Time-to-clear/nearly clear (investigator's assessment; follow-up 4-8 weeks)									
1 Langley 2011A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	183	**Clear/nearly clear (IGA)** Week 4 34 (18.6%) Week 8 73 (39.9%)	⊕⊕OO LOW
Time-to-clear/nearly clear (investigator's assessment; follow-up 4-8 weeks)									
1 Fleming	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	162	**Clear/nearly clear (IGA)**	⊕⊕OO LOW

2010A								Week 4 26 (16.0%) Week 8 44 (27.2%)	
Time-to-clear/nearly clear (patient's assessment; follow-up 4-8 weeks)									
1 Langley 2011A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	183	Clear/nearly clear (patient rating) Week 4 52/175 (29.7%) Week 8 69/171 (40.4%)	⊕⊕OO LOW
Time-to-maximum effect (% change in PASI; follow-up 4-8 weeks)									
1 Langley 2011A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	183	% change in PASI Week 4 -53.1 Week 8 -57.0	⊕⊕OO LOW
Time-to-maximum effect (% change in PASI; follow-up 2-4 weeks)									
1 Ortonne 2004	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	249	Mean % reduction in PASI score from baseline 2 weeks 50.5% 4 weeks 65.0%	⊕⊕OO LOW
Time-to-maximum effect (change in PASI; follow-up 2-4 weeks)									
1 Saraceno 2007	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75	**Mean PASI (SD)** Baseline 9.49 (5.39) 2 weeks 3.81 (3.27) 4 weeks 2.50 (2.50)	⊕⊕OO LOW
Mean time to maximum response (IAGI) (follow-up 52 weeks)									
1 Kragballe 2006	observational studies[a]	no serious risk of bias[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	212	Graph of % satisfactory responses by investigator assessment shows that maximum response is achieved by 12 weeks	⊕OOO VERY LOW

1 *(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the*
2 *comparator arm*

(b) Unclear allocation concealment may have biased patient selection for this intervention
(c) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (33.3%)
(d) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (30.2%)
(e) Interpreted from graphical representation

8.2.4.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for a combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate; no statistical analysis could be performed).

In people with psoriasis, the time to remission when using a combined product containing vitamin D or vitamin D analogue and potent corticosteroid (calcipotriol plus betamethasone dipropionate) varied between studies:

- Proportion achieving remission (investigator's or patient's assessment) by 8 weeks ranged from 27.2 to 40.4% [2 studies; 345 participants; low quality evidence][169,184]
- The continued increase in responders (investigator's or patient's assessment) between 4 and 8 weeks ranged from 10.7-21.3% [2 studies; 345 participants; low quality evidence][169,184]
- Of those who achieved remission by the end of the trial, 46.6-59.1% had responded by week 4 based on Investigator's assessment, but the figure was 75.4% based in patient's assessment [2 studies; 345 participants; low quality evidence][169,184]
- The decrease in PASI from 2-4 weeks ranged from 14.5-14.7% [2 studies; 324 participants; low quality evidence][199,203]
- The decrease in PASI from 4-8 weeks was 3.9% [1 study; 183 participants; low quality evidence][169]
- Graphical representation of longer-term data demonstrated that the maximum rate of satisfactory responses based on investigator assessment score was achieved by 12 weeks based on once daily administration as needed, with negligible further improvement up to 12 months [1 study; 212 participants; very low quality evidence][192]

Summary

The evidence suggests that maximum response is not achieved in all patients by 4-8 weeks, with the response rate still increasing slightly at this time point. One study[192] suggested that 12 weeks may represent the time at which maximum achievement of satisfactory response is achieved based on once daily administration of a combined product containing calcipotriol monohydrate and betamethasone dipropionate as needed, although there was only minimal improvement after 4 weeks.

1

8.2.5 Concurrent potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening)

8.2.5.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concurrent		
Time-to-maximum response (change in PASI; follow-up 4 weeks)									
1 Ruzika 1998	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	Calcipotriol + betamethasone valerate 78	Based on PASI score over time maximum effect was not reached by 4 weeks of concurrent treatment in the randomised phase (following 2 weeks of calcipotriol treatment)	⊕OOO VERY LOW
Time-to-maximum response (change and % change in PASI; follow-up 8 weeks)									
1 Kragballe 1998	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	Calcipotriol + betamethasone valerate 176	Based on change in PASI (and % change in PASI) maximum treatment effect had not been reached by 8 weeks	⊕OOO VERY LOW
Time-to-maximum response (change in PASI; follow-up 4 weeks)									
1 Salmhofer 2000	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	Calcipotriol + diflucortolone valerate 63	Based on mean PASI, rapid improvement was seen over first 2 weeks but continued gradual improvement seen up to 4 weeks (maximum effect not reached)	⊕OOO VERY LOW

4 *(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the*
5 *comparator arm*
6 *(b) Unclear allocation concealment may have biased patient selection for this intervention*
7 *(c) Interpreted from graphical representation*

8

8.2.5.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for concurrent potent corticosteroid and vitamin D or vitamin D analogues (one applied in the morning and one in the evening; no statistical analysis could be performed).

In people with psoriasis, the time to remission when using concurrent potent corticosteroid and vitamin D or vitamin D analogues (one applied in the morning and one in the evening):

- Mean change (or % change) in PASI showed that a maximum effect was not reached by week 4 or 8 [3 studies; 317 participants; very low quality evidence][173,190,202]

Summary

The evidence suggests that maximum response is not achieved in all patients by 4-8 weeks, with the response rate still increasing at this time point based on PASI score.

8.2.6 Coal tar

8.2.6.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Coal tar		
Mean time to maximum response (% change in PASI) (follow-up 6 weeks)									
1 Thawornchaisit 2007	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10% liquor carbonis detergens 28	Mean PASI and % change in PASI score from baseline 2 weeks 14.83±3.0 -13.56±8.5% 4 weeks 12.31±3.3 -28.18±16.5% 6 weeks 10.60±4.1	⊕⊕OO LOW

								-38.39±21.1%	
Mean time to maximum response (% change in PASI) (follow-up 6 weeks)									
1 Tham 1994	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Liquor picis carbonis 27	Mean PASI and % change in PASI score from baseline Baseline 12.95±3.4 2 weeks 5.9±4.5 -9.4±15.9% 4 weeks 5.1±4.2 -22.3±24.2% 6 weeks 4.5±3.6 -30.9±24.6%	⊕⊕OO LOW
Mean time to maximum response (% change in mPASI [0-64.8]) (follow-up 12 weeks)									
1 Alora-Palli 2010	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Liquor carbonis detergens 27	% change in PASI (0-64.8) from baseline Baseline 7.3 4 weeks 4.69 (-35.4%) 8 weeks 3.70 (-48.9%) 12 weeks 3.24 (-58.2%)	⊕⊕OO LOW
Mean time to maximum response (TSS; follow-up 8 weeks)									
1 Pinheiro 1997	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	very serious[c]	very serious[d]	none	Alphosyl HC 65	The maximum response based on mean TSS was seen at 4 weeks, with no further improvement up to 8 weeks	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm

(b) Unclear allocation concealment may have biased patient selection for this intervention

(c) Incorrect outcome measure

(d) Interpreted from graphical representation

8.2.6.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for coal tar (no statistical analysis could be performed).

In people with psoriasis, the time to remission when using coal tar varied between studies:

- The continued % decrease in PASI from 2-4 weeks ranged from 12.9-14.62% (0.8-2.52 PASI points) [2 studies; 55 participants; low quality evidence][205,206]
- The continued % decrease in PASI from 4 to 6 or 8 weeks ranged from 8.6-13.5% (0.6-1.71 PASI points) [3 studies; 82 participants; low quality evidence][157,205,206]
- The decrease in PASI from 8-12 weeks was 9.3% (0.46 PASI points) [1 study; 27 participants; low quality evidence][157]
- Mean change in TSS demonstrated that the maximum response was achieved by 4 weeks, with negligible further improvement up to 8 weeks [1 study; 65 participants; very low quality evidence][172]

Summary

The evidence suggests that maximum response to LCD or LPC based on PASI is not achieved in all patients by 6-12 weeks, although the continued absolute change in PASI is small. However, based on TSS, maximum response was seen at 4 weeks when using the Alphosyl HC formulation.

8.2.7 Dithranol

8.2.7.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dithranol		
Mean time to maximum response (change in global improvement score; follow-up 8 weeks)									
1 Hutchinson 2000	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	0.25-2.0% cream (for 30 mins) 60	Based on change in global improvement score over time the maximum treatment effect had not been reached by 8 wks, although the most rapid improvement was seen over the first 4 weeks, with much more gradual reduction between 4-8 wk	⊕OOO VERY LOW

Mean time to maximum response (mean PASI) (follow-up 8 weeks)									
1 Hutchinson 2000	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	0.25-2.0% cream (for 30 mins) 60	Based on mean PASI, maximum effect appeared to be reached between weeks 6 and 8	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm
(b) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (29.6%)
(c) Interpreted from graphical representation
(d) Unclear allocation concealment may have biased patient selection for this intervention
(e) Incorrect outcome measure

8.2.7.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for dithranol (no statistical analysis could be performed).

In people with psoriasis, the time to remission when using dithranol was as follows:

- Mean change in global improvement showed that a maximum effect was not reached by week 8 [1 study; 60 participants; very low quality evidence][186]
- Mean change in PASI showed that a maximum effect was reached by week 6-8 [1 study; 60 participants; very low quality evidence][186]

Summary

The evidence suggests that maximum response to dithranol is achieved by 8 weeks of treatment based on change in PASI, but not when assessed using a global improvement score, although even on this outcome the most rapid and pronounced improvement was seen over the first 4 weeks[186].

8.2.8 Tazarotene

8.2.8.1 Evidence profile

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tazarotene		
Time-to-remission (at least good improvement; follow-up 12 weeks)									
1 Weinstein 1997	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[c]	very serious[d]	none	211	Based on graphical representation of the % with good or excellent improvement or clearing the maximum response rate had not been reached by 12 weeks	⊕OOO VERY LOW
Time-to-remission (none, minimal or mild disease; follow-up 12 weeks)									
1 Weinstein 2003	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[c]	very serious[d]	none	439	Based on graphical representation of the % with none, minimal or mild disease the maximum response rate had not been reached by 12 weeks	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm

(b) Unclear allocation concealment may have biased patient selection for this intervention

(c) Incorrect definition of response

(d) Interpreted for graphical representation

8.2.8.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for tazarotene (no statistical analysis could be performed).

In people with psoriasis, the time to remission when using tazarotene was as follows:

- Proportion achieving remission had not reached a maximum by 12 weeks [2 studies; 650 participants; very low quality evidence][178,208]

Summary

The evidence suggests that maximum proportion achieving remission was not achieved by 12 weeks.

8.3 Network meta-analysis (trunk and limbs)

Based on the results of conventional meta-analyses of direct evidence alone, it can be difficult to determine which intervention is most effective in the treatment of chronic plaque psoriasis. The challenge of interpretation arises for two reasons:

- Some pairs of alternative strategies have not been directly compared in a randomised controlled trial (for example, concurrent vitamin D or vitamin D and potent corticosteroid [one applied in the morning and one in the evening] vs a combined product containing vitamin D or vitamin D analogue and potent corticosteroid)
- There are frequently multiple overlapping comparisons (for example vitamin D or vitamin D analogue vs potent corticosteroid, vitamin D or vitamin D analogue vs a combined product containing vitamin D or vitamin D analogue and potent corticosteroid and potent corticosteroid vs a combined product containing vitamin D or vitamin D analogue and potent corticosteroid) that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy, defined as the achievement of clearance or near clearance. A network meta-analysis also provides estimates of effect (with 95% credible interval) for each intervention compared to one another and compared to a single baseline risk. These estimates provide a useful and coherent clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness of the topical therapies in the original cost-effectiveness modelling outlined in section 8.4. For details on the methods, results and interpretation of the network meta-analyses, see Appendix K.

The inclusion criteria for and intervention compared in the NMA were the same as in the review of direct evidence (Section 8.1.1). A class effect was still assumed, but in order to reduce heterogeneity in the network of evidence, interventions were broken down by treatment frequency from the outset. In other words, once daily vitamin D or vitamin D analogue and twice daily vitamin D or vitamin D analogue were considered separate comparators in the NMA. Placebo/vehicle delivered once daily was also considered separately from twice daily placebo/vehicle.

The outcomes considered as part of the NMA were restricted to those measuring response:

- Clear/nearly clear or marked improvement (at least 75% improvement) on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)
- Clear/nearly clear or marked improvement (at least 75% improvement) on Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment

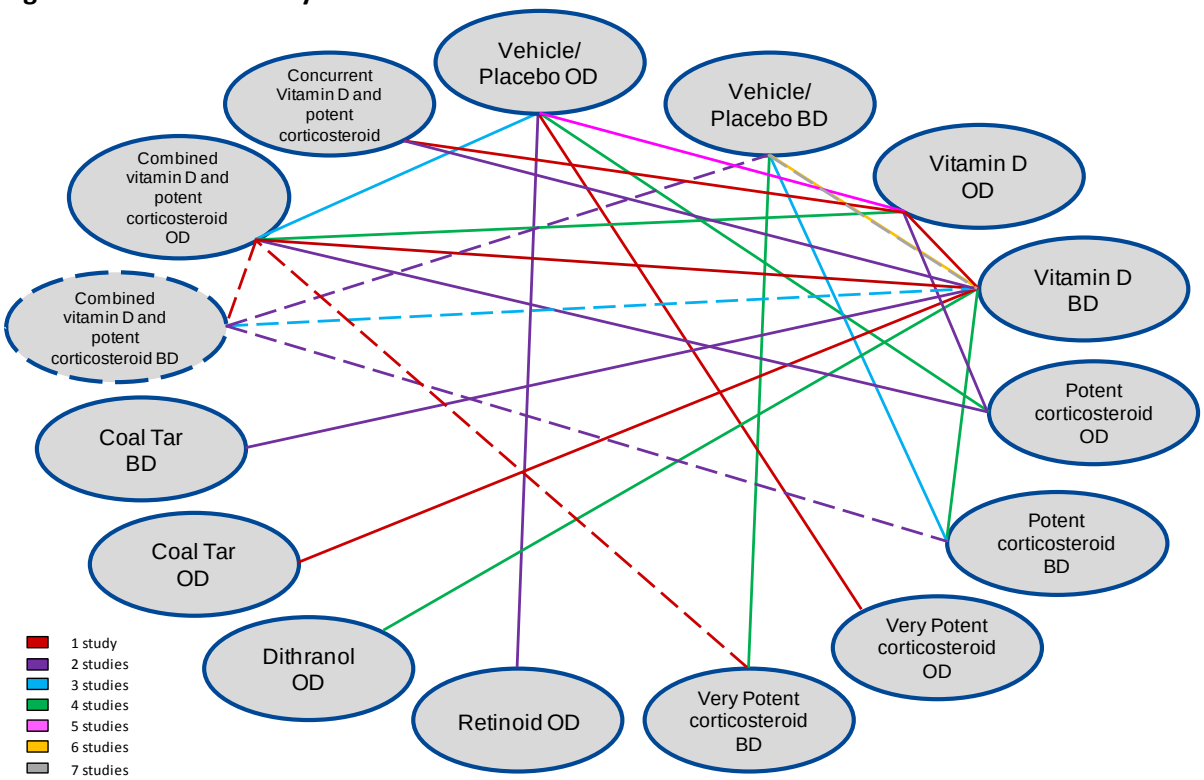
Some included studies will have reported both outcomes, whereas some will have only included one or the other. For this reason, two networks of evidence were developed and analysed.

8.3.1 Results of NMA for investigator assessed outcome: clear/nearly clear (IAGI/PGA)

Thirty-five studies[157-159,162-164,166,167,169-172,174,180,182-187,189,190,194-197,199-202,205,207-209] met the inclusion criteria for the base case network meta-analysis of the investigator assessed outcome of clear/nearly clear. Three further studies[25,198,206] were included in a sensitivity analysis, the details and results of which can be found in Appendix K.

Figure 1 presents all the interventions included in the NMA as well as shows where there is direct evidence for a particular comparison and the number of studies that have included that comparison. For example, there are 7 studies reporting the outcome 'clear' or 'nearly clear' as measured by IAGI or PGA for the comparison of twice daily vehicle/placebo and twice daily vitamin D or vitamin D analogue. The diagram also highlights where there are gaps in the direct evidence. For example, there are no studies comparing a combined product containing vitamin D or vitamin D analogue and potent corticosteroid to concurrent vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening).

Figure 3: Clear or nearly clear – IAGI and PGA



Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the base case. Dashed lines indicate all head-to-head comparisons included in the sensitivity analysis, details and results of which can be found in Appendix K.

The results of the network meta-analysis in terms of the relative risk of each intervention compared to twice daily vehicle/placebo are presented in Table 62. It also gives a probability that the intervention is the most effective overall.

Table 62: Relative risks of clear/nearly clear on IAGI/PGA for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective
Very potent corticosteroid BD	6.095	4.507	7.102	48.5%
Combined vitamin D or vitamin D analogue and potent corticosteroid OD	5.533	3.488	6.824	12.8%
Very potent corticosteroid OD	5.302	1.495	7.369	25.6%
Concurrent vitamin D or vitamin D analogue and	5.1	2.863	6.726	7.7%

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective
potent corticosteroid				
Potent corticosteroid BD	4.877	3.435	6.093	1.8%
Coal Tar BD	4.279	1.924	6.426	3.1%
Vitamin D or vitamin D analogue BD	4.251	3.074	5.368	0.0%
Potent corticosteroid OD	3.73	1.469	6.006	0.1%
Vitamin D or vitamin D analogue OD	3.393	1.586	5.529	0.0%
Dithranol OD	3.357	1.688	5.266	0.1%
Retinoid OD	2.099	0.4376	5.387	0.1%
Coal Tar OD	0.9658	0.1153	4.127	0.1%
Placebo OD	0.7629	0.2107	2.162	0.0%

8.3.111 Evidence statements

Results of the network meta-analysis of randomised controlled trials indicate that, compared to twice daily vehicle/placebo, the following interventions are statistically significantly more effective at inducing clearance/near clearance as measured by the investigator or physician (IAGI/PGA):

- Once and twice daily very potent corticosteroid
- Once and twice daily potent corticosteroid
- Once and twice daily vitamin D or vitamin D analogue
- Once daily dithranol
- Twice daily coal tar
- Vitamin D or vitamin D analogue and potent corticosteroid (combined in one product)
- Vitamin D or vitamin D analogue and potent corticosteroid (applied separately – one in the morning, one in the evening)

Results of the network meta-analysis of randomised controlled trials indicate that, compared to twice daily vehicle/placebo, the following interventions are not statistically significantly more effective at inducing clearance/near clearance as measured by the investigator or physician (IAGI/PGA):

- Once daily retinoid
- Once daily coal tar

Results of the network meta-analysis indicate that there are very few comparisons between active treatments (i.e. anything other than vehicle/placebo) for which the treatment effect reaches statistical significance. A few exceptions include:

- Twice daily very potent corticosteroid and once daily product containing calcipotriol monohydrate and betamethasone dipropionate are more effective than once daily vitamin D or vitamin D analogue.
- Once daily product containing calcipotriol monohydrate and betamethasone dipropionate is more effective than once daily potent corticosteroid and once daily retinoid.
- Twice daily very potent corticosteroid is more effective than once daily retinoid and once daily dithranol.
- Twice daily vitamin D or vitamin D analogue, twice daily potent corticosteroids, twice daily very potent corticosteroids, combined and concurrent vitamin D or vitamin D analogue and potent corticosteroids are all more effective than once daily coal tar.

Results indicate that there is a non-statistically significant trend for twice daily application of any topical to be more effective than once daily application of the same topical.

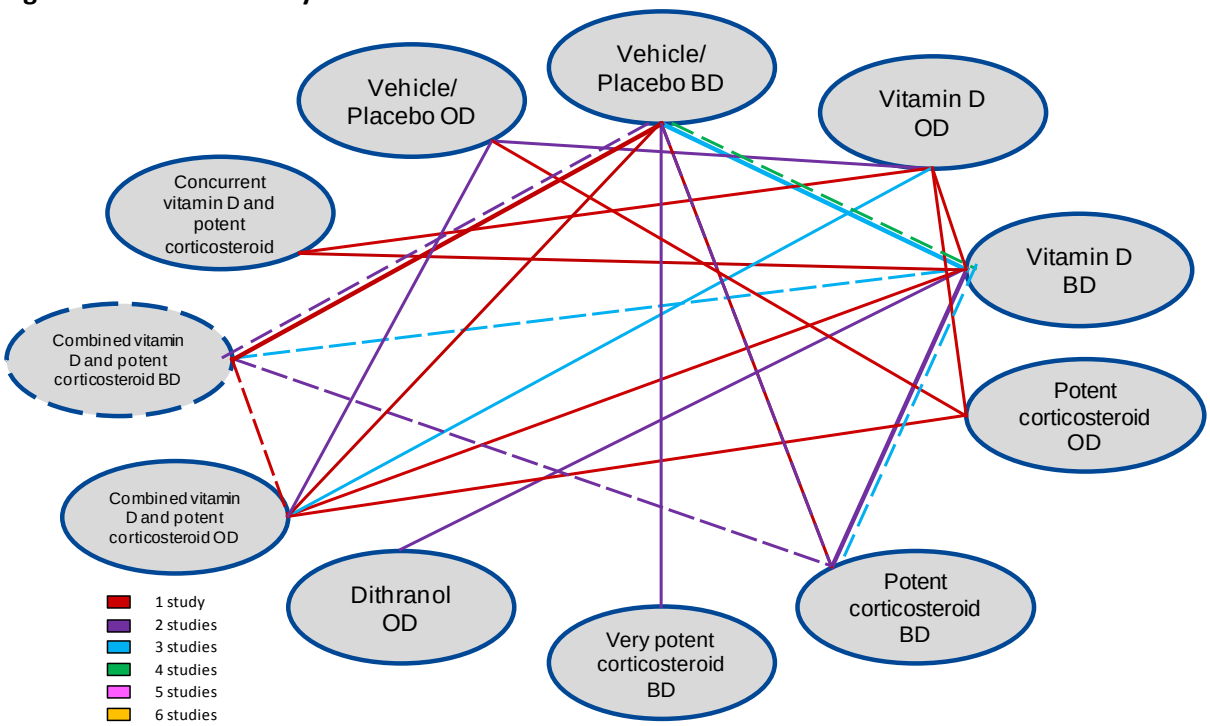
Details of the pairwise comparisons from the network meta-analysis can be found in appendix X.

8.3.2 Results of NMA for patient assessed outcome: clear/nearly clear (PAGI)

Fourteen studies[159,164,165,168,169,174,181,183,185,189,190,196,199,207] met the inclusion criteria for the base case network meta-analysis of the patient assessed outcome of clear/nearly clear. Two further studies[25,200] were included in a sensitivity analysis, the details and results of which can be found in Appendix X.

Figure 4 presents all the interventions included in the NMA as well as shows where there is direct evidence for a particular comparison and the number of studies that have included that comparison. From the diagram, one can see that fewer studies have reported PAGI. There are 4 studies reporting the outcome of 'clear' or 'nearly clear' as measured by PAGI (in contrast to 7 studies reporting for IAGI or PGA) for the comparison of twice daily vehicle/placebo and twice daily vitamin D or vitamin D analogue.

Figure 4: Clear or nearly clear - PAGI



Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the base case. Dashed lines indicate all head-to-head comparisons included in the sensitivity analysis, details and results of which can be found in Appendix X.

The results of the network meta-analysis in terms of the relative risk of each intervention compared to twice daily vehicle/placebo are presented in Table 63. It also gives a probability that the intervention is the most effective overall.

Table 63: Relative risks of clear/nearly clear with PAGI for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective
Combined product containing calcipotriol monohydrate and betamethasone dipropionate OD	4.632	2.856	5.861	51.54%
Concurrent vitamin D or vitamin D analogue and potent corticosteroid	4.224	1.854	5.915	27.64%
Potent corticosteroid OD	3.852	1.504	5.823	12.24%
Vitamin D or vitamin D analogue BD	3.56	2.161	4.922	1.57%
Potent corticosteroid BD	3.294	1.73	4.967	2.80%
Very potent corticosteroid BD	2.654	1.092	4.649	3.69%
Vitamin D or vitamin D analogue OD	2.451	0.9893	4.428	0.01%
Dithranol OD	2.287	0.8306	4.436	0.50%
Placebo OD	1.549	0.4531	3.798	0.01%

8.3.231 Evidence statements

Results of the network meta-analysis of randomised controlled trials indicate that, compared to twice daily vehicle/placebo, the following interventions are statistically significantly more effective at inducing clearance/near clearance as measured by the patient (PAGI):

- Twice daily very potent corticosteroid
- Once and twice daily potent corticosteroid
- Twice daily vitamin D or vitamin D analogue
- Vitamin D analogue and potent corticosteroid (combined in one product)
- Vitamin D or vitamin D analogue and potent corticosteroid (applied separately – one in the morning, one in the evening)

Results of the network meta-analysis of randomised controlled trials indicate that, compared to twice daily vehicle/placebo, the following interventions trend toward being more effective at inducing clearance/near clearance as measured by the patient (IAGI/PGA), but the results fail to reach statistical significance:

- Once daily vitamin D or vitamin D analogue
- Once daily dithranol

Results of the network meta-analysis indicate that there are very few comparisons between active treatments (i.e. anything other than vehicle/placebo) for which the treatment effect reaches statistical significance. The one exception includes:

- Once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate is more effective than once daily vitamin D or vitamin D analogue and more effective than once daily dithranol.

Details of the pairwise comparisons from the network meta-analysis can be found in appendix K.

8.4 Cost effectiveness evidence (trunk and limbs)

8.4.1 Economic evidence – literature review

An economic evaluation should ideally compare all relevant alternatives. No applicable studies of good enough methodological quality were identified comparing all interventions of interest –vitamin D or vitamin D analogues, potent or very potent corticosteroids, coal tar, dithranol and retinoids – in the treatment of patients with mild to moderate chronic plaque psoriasis.

Three studies[212-214] were identified that included two or more of the relevant comparators. These are summarised in the economic evidence profile below (Table 64 and Table 65). See also the full study evidence tables in Appendix I.

Six studies were selectively excluded, four due to very serious methodological limitations[215-218] and two due to the availability of more applicable economic evidence[219,219,220,220]. Reasons for their exclusion are provided in Appendix G.

Table 64: Calcipotriol versus short contact dithranol – Economic study characteristics

Study	Limitations	Applicability	Other comments
Ashcroft 2000	Potentially serious limitations (a)	Partially applicable (b)	A decision analytic model using a NHS payer perspective.
Bottomley 2007	Potentially serious limitations (c)	Directly applicable (d)	CUA based on indirect published data. Scottish payer perspective.
Oh 1997	Potentially serious limitations (e)	Partially applicable (f)	CUA based on meta-analysis. Canadian payer perspective

(a) Response estimates taken from single RCT[207] included in clinical review; relapse estimates taken from RCT[221] not included in clinical review. Unclear if time horizon sufficient to capture all downstream effects and costs, resulting in possible insufficient attention paid to treatment failures. Limited sensitivity analysis.
(b) Appropriate population (mild to moderate plaque psoriasis).From UK NHS perspective and 2000 UK pounds. Does not include all relevant comparators for the question. No quality of life assessment.
(c) Sufficient time horizon of 1 year. Important and relevant health outcomes included. Serious limitations in the methodology and source used to generate treatment effect. Source for resource use and unit costs seem reasonable.
(d) Scottish NHS perspective. Appropriate population. Relevant direct health effects and costs considered. Quality of life assessment presumed to use EQ-5D.Interventions appropriate for the guideline.
(e) Sufficient time horizon of 1 year. Unclear if best estimates of resource use, costs and treatment effect used, expert panel used. Costs may now be outdated (1992 and 1995).Limited sensitivity analysis.
(f) Canadian government paying perspective with costs from 1996 price level. Compares calcipotriol to corticosteroids post treatment with betamethasone valerate.

Table 65: Calcipotriol(a)versus short contact dithranol(b) – Economic summary of findings

Study	Incremental cost	Incremental effects (c)	Incremental Cost effectiveness	Uncertainty
Ashcroft (12 weeks)	£64.68(d)	11.2% more successes (e)	£577.50 per additional success	A limited one way sensitivity analysis explored efficacy and cost estimates, however its simplicity makes meaningful interpretation difficult. Results are presented in section 1.3.
Ashcroft (1 year)	£38.66 (d)	No difference in success rate 1.94 days with success	Dithranol dominates £19.93 per additional	

Study	Incremental cost	Incremental effects (c)	Incremental Cost effectiveness	Uncertainty
			day with success	

(a) Calcipotriol applied twice daily (estimated weekly dosage of 34.2g).
(b) Dithrocream 2% applied once daily (assumed weekly dosage was half of twice daily calcipotriol dosage: 17.1g/wk) [N.B. due to a paucity of data, relapse rates of micranol cream were used to represent those of short contact dithranol].
(c) Effectiveness measured as proportion achieving 'success' or 'no relapse' in short 12-week time horizon and 1 year time horizon; effectiveness also measured as' days with success' for 1-year time horizon.
(d) Direct costs based on unit cost of NHS drug treatments form the Monthly Index of Medical Specialities. Physician consultations and dispensing fees were not included as assumed to be similar for both interventions.
(e) "Success" defined as ≥75% improvement from baseline; based on a 5 point patient rated scale (completely cleared, marked improvement, some improvement, no change, worse). Relapse defined as change from the end of treatment of 3 grades or more in the investigators response.

Ashcroft and colleagues present a simple decision tree analytic model to explore the relative cost effectiveness of topical calcipotriol and short contact dithranol. Caution should be exercised when interpreting the results of this study as it is unclear if the best possible sources were used to inform the parameters, and the short time horizon means that the costs of treatment failure may have not been fully accounted for.

Ashcroft et al. did not perform a quality of life assessment which limits its usefulness in determining cost effectiveness of the interventions studied. The below table shows the results of Ashcroft et al., with estimates of the possible incremental cost effectiveness ratio over a 1-year time horizon had quality of life measurements been incorporated. The ICERs presented below show that if utility gains of 0.03 or 0.09 are assumed (based on estimates used by other authors[213,214] in the economic review) the additional cost of calcipotriol is very unlikely to be offset by the additional benefits associated with this treatment.

Table 66: Economic summary of Ashcroft et al. findings with quality of life incorporated

Comparison	Incremental cost	Utility gain applied	Incremental effects	ICER
Calcipotriol Vs. short contact dithranol therapy (1 year horizon)	£38.66	N/A	1.94 successful days (0.0053 years)	It costs £19.93 per additional successful day when using calcipotriol compared to dithranol
		0.09 (a)	0.0005 QALYs	£77,320 per QALY
		0.03 (b)	0.0002 QALYs	£243,145 per QALY

(a) Utility gains based on those presented by Bottomley and colleague[213]s who estimated the utility gain of achieving a PASI75 to be 0.09.
(b) Utility gains based on those presented by Oh and colleagues[214] who estimated the utility gain of achieving 'success' defined as a 'sufficient improvement in disease activity to allow the initial dosage of drug to be reduced to maintenance level (i.e. 75% of the initial dosage).'

Table 67: Vitamin D or vitamin D analogues vs potent corticosteroids vs combined and concurrent vitamin D or vitamin D analogues and potent corticosteroids (one applied in the morning and one in the evening) - Economic summary of findings

Study	Interventions compared	Incremental cost	Incremental effects (QALYS)	Incremental Cost effectiveness	Uncertainty

Study	Interventions compared	Incremental cost	Incremental effects (QALYS)	Incremental Cost effectiveness	Uncertainty
Bottomley and colleagues (a)					
1.TCF OD (8 wks) 2. Vit D OD (4wks)→BDP OD (4wks) 3. Vit D BD (4wks) → BDP OD(4wks) 4. BDP OD(4wks) → Vit D OD (4wks) 5. Concurrent Vit D (morning) & BDP (evening) (8 wks)		1. least cost 2. £138 3. £97 4. £133 5. £276	1. most effective 2. -0.013 3. -0.011 4. -0.012 5. -0.018	TCF OD (8 wks) dominates all other treatments	The results were sensitive to changes in the cost second-line treatment with phototherapy, cost of TCF, baseline utility and utility enjoyed whilst on the phototherapy waiting list.
Oh and colleagues (b),(c)					
1. BMV (6 wks)→ CLO (2 wks) 2. BMV (6 wks)→ CLO (4 wks) 3. BMV (6 wks)→ Vit D (6wks) 4.BMV (6 wks)→ CLO (6 wks) Secondary analysis for patients that have failed BV 1B: F (0.05%) 2B: BMD 3B: Vitamin D or vitamin D analogue		1: least cost 2: £72 3: £140 (d) 4: £4 1B: least cost 2B: £67 3B: £70 (e)	1: 2nd most effective 2: -0.0096 3: 0.0049 (d) 4: -0.0241 1B: 2nd most effective 2B: -0.0299 3B: 0.0118 (e)	1. NA 2. dominated 3. £28,571(d) 4. dominated 1B: NA 2B: dominated 3B: £5,932 (e)	The results were sensitive to cost and quantity of calcipotriol used, if the amount of calcipotriol reduced from 45g to 30.6g, the calcipotriol strategy (intervention 1) was dominant (less costly and more effective). Analysis also sensitive to utility associated with side effects of F, whereby if patients on F and CAL had similar associated utility, F became the dominant strategy.

OD=once daily; BD=twice daily; BMV = betamethasone valerate; BDP= betamethasone dipropionate; CAL = Calcipotriol; TCF=two compound formulation containing calcipotriol monohydrate and betamethasone dipropionate; AE = adverse event; q=for; wk = week; CLO =Clobetasol propionate; F = Fluocinonide; PPP=purchasing power parities.

(a) Costs incorporated topical treatments, GP consultation, specialist outpatient consultation and course of phototherapy. These costs were estimated using: MIMS, PSSRU, Scottish reference costs.

(b) BMV was at 0.1% strength, CLO=0.05% strength. For all comparators BMV was given at 60g, and at 45g/wk for remainder of year if successful. If unsuccessful, the patient continued to second line therapy. CLO was given at 0.05% and 50 mg/wk.

(c) Costs included topical corticosteroids, physician fees, laboratory tests, UVB therapy and PUVA. These costs were estimated using the Ontario Drug Benefit Formulary (1995), the OHIP Fee Schedule (1992), published source, expert panel and Leo Laboratory in the case of calcipotriol.

(d) Compared to next less costly, non-dominated strategy, comparator 1.

(e) Compared to next less costly, non-dominated strategy, comparator 1B.

Both studies identified had potentially serious limitations with their chosen methodology. Bottomley and colleagues used an NHS provider perspective and was directly applicable, but is limited by the method used to generate estimates of treatment effect. The authors used performed an unadjusted indirect comparison which may introduce bias. The sensitivity analyses conducted by Bottomley et al. provide some indication that once daily product containing calcipotriol monohydrate and betamethasone dipropionate may be a cost effective strategy provided that the difference in utility between baseline and that experienced on the waiting list is small (i.e. 0.075). Interestingly, Bottomley and colleagues found concurrent but separate treatment with vitamin D or vitamin D analogue and potent corticosteroids to be the most expensive strategy and provided the least QALYs.

Oh and colleagues considered separate second line treatments when a first line treatment of a medium potency corticosteroid (betamethasone valerate) failed. Their evidence suggests that where the needed dosage and length of treatment of calcipotriol is similar or less than the ultra high potency corticosteroid clobetasol propionate, then calcipotriol might be the more cost effective second line treatment, however its incremental cost effectiveness compared to 2 weeks of very potent steroid was over the NICE £20,000 per QALY threshold. Calcipotriol performed better as a primary treatment for psoriasis which was resistant to betamethasone valerate, with increased utility due to lower side effects compared to flucoinonide.

8.4.2 Economic evidence – original economic analysis

The review of clinical evidence for topical therapies used in the treatment of individuals with mild to moderate plaque psoriasis showed that there were a wide variety of options – emollients, tars, dithranol, retinoids, corticosteroids (potent and very potent), vitamin D or vitamin D analogues and combination products – each associated with certain advantages and disadvantages. The results of the network meta-analysis suggested that some interventions, such as combined or concurrent vitamin D analogue and potent corticosteroid, were more likely to induce clearance or near clearance than others. Given that these combined and concurrent application strategies carry additional cost compared to both their individual constituent parts and compared to other topical alternatives, it was important to consider whether these additional costs are justified by additional health benefits in terms of improved quality of life.

The choice of which topical therapy to offer patients with mild to moderate psoriasis in primary care was identified as among the highest economic priorities by the GDG because the greatest proportion of psoriasis patients are managed at this point in the care pathway. Even if the unit costs of the interventions are quite modest, the population affected is relatively large; therefore the health economic impact of any recommendation is likely to be substantial.

Three cost-effectiveness analyses were identified in the published literature, but each had methodological limitations that called its conclusions into question. The analysis by Ashcroft and colleagues[212] was based on only one trial and included only two of the interventions of interest (dithranol and calcipotriol). The analysis by Oh and colleagues[214] was quite old and had a fairly confusing model structure. The analysis by Bottomley and colleagues,[213] although the most applicable of the included studies, used an unadjusted indirect comparison to inform the treatment effect estimates, which likely overestimated the effectiveness of some interventions and underestimated the effectiveness of others. Bottomley and colleagues also did not include all the possible comparators of interest. Due to the methodological limitations of the published economic analyses, there was still substantial uncertainty as to which topical therapy or therapies represented the best value for NHS resources. In order to reduce this uncertainty, an original cost-effectiveness analysis was undertaken by the guideline health economist in collaboration with the GDG. Below is a summary of the analysis that was undertaken. For full details please see Appendix M: Cost-effectiveness analysis.

8.4.211 Methods

An analysis was undertaken to evaluate the relative cost-effectiveness of different topical therapy sequences used in the treatment of individuals with mild to moderate chronic plaque psoriasis. A Markov model was used to estimate 12-month costs and quality-adjusted life years (QALYs) from a current UK NHS and personal social services perspective. A 12-month time horizon was considered clinically relevant and sufficiently long enough to capture important costs and consequences of first-line treatment in primary care. Uncertainty was explored through probabilistic analysis and sensitivity analysis. The performance of alternative treatment sequences was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness.

The aim of the analysis was to identify the most cost-effective sequence of first, second and third line topical therapies. It was important to model sequences given that most patients will commence treatment with one topical and then try others before moving on to more intensive treatments such as phototherapy and/or systemic therapy. In all, 122 sequences were compared in the base case analysis. Table 68 presents the list of possible first, second and third line treatments which may be combined in a sequence.

Table 68: All possible sequences of first, second and third line interventions

First line	Second line	Third line
Vitamin D or vitamin D analogue OD	Vitamin D or vitamin D analogue OD	Vitamin D or vitamin D analogue OD
Vitamin D or vitamin D analogue BD	Vitamin D or vitamin D analogue BD	Vitamin D or vitamin D analogue BD
Potent corticosteroid OD	Potent corticosteroid OD	Potent corticosteroid OD
Potent corticosteroid BD	Potent corticosteroid BD	Potent corticosteroid BD
Combined product containing calcipotriol monohydrate and betamethasone dipropionate OD	Combined product containing calcipotriol monohydrate and betamethasone dipropionate OD	Combined product containing calcipotriol monohydrate and betamethasone dipropionate OD
Concurrent am/pm	Concurrent am/pm	Concurrent am/pm
		Dithranol OD
		Coal tar BD
		Referral

The following conditions were placed on the sequences, ensuring that they represented logical clinical practice:

- Concurrent treatment with vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening) would not come after a failure of once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate;
- Once daily treatment with a given topical would not come after a failure of twice daily treatment with the same topical;
- Once daily treatment with potent steroid or vitamin D or vitamin D analogue would not come after concurrent treatment with vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening) or once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate;
- No strategy could include potent corticosteroids among all three lines of treatment (including as part of concurrent vitamin D or vitamin D analogues and potent corticosteroid (one applied in the

morning and one in the evening) or combined product containing calcipotriol monohydrate and betamethasone dipropionate).

Most comparators focus on evaluating a trial of three different treatments before referral for specialist review, but the GDG was also interested in whether earlier escalation of care might be more cost-effective. To test this, strategies have also been combined into two-treatment sequences with referral following a failure of second line treatment.

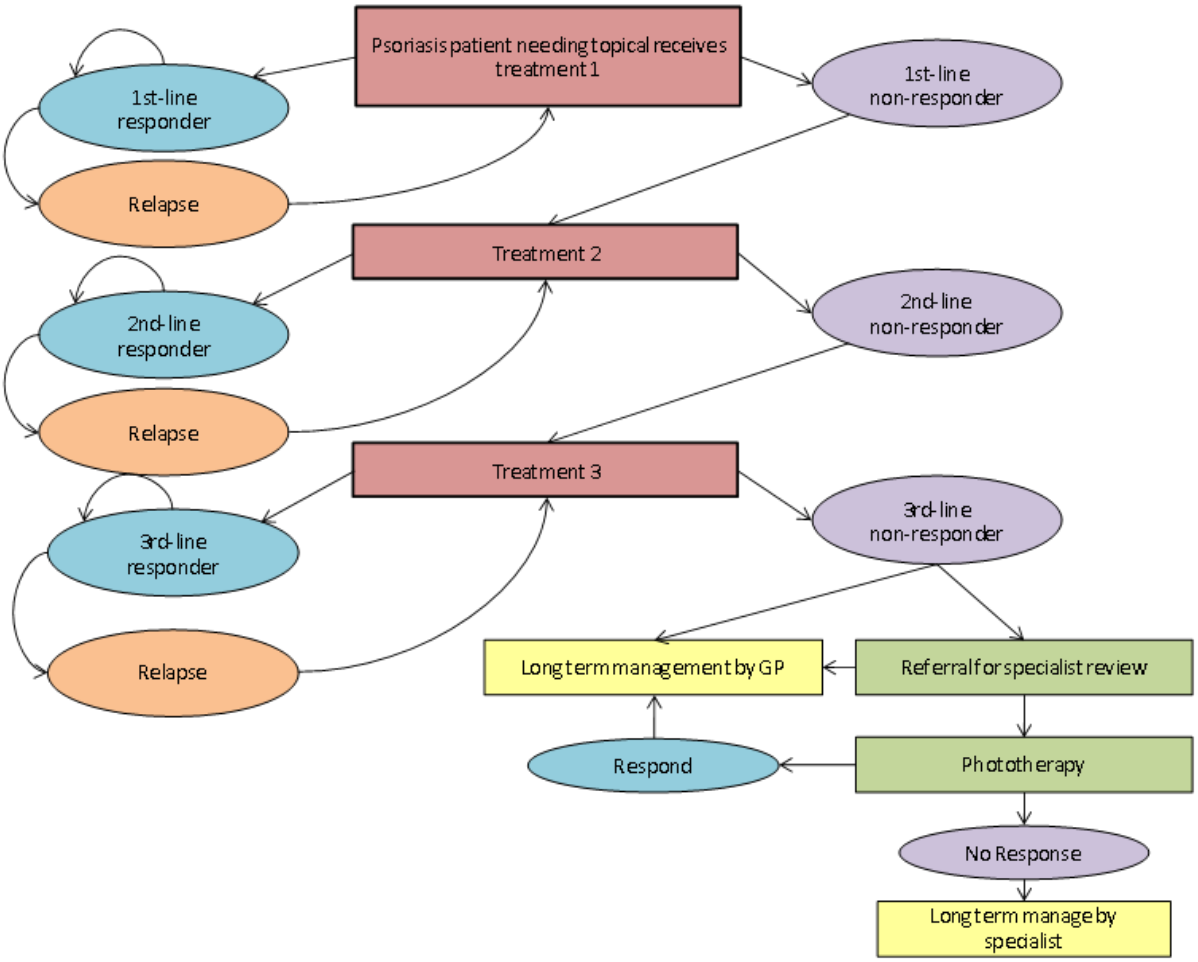
Due to the unacceptability of dithranol and coal tar as routine treatments (difficult application, risk of staining, strong and unpleasant odours, etc), these treatments were reserved for third line treatment only. This reflects their current placement in primary care given the availability of more acceptable and effective topicals such as those being compared as first and second line topicals. In a series of sensitivity analyses, other restrictions were placed on the potential sequences, namely due to concerns about the safety of continued use of potent corticosteroids.

The structure of the model developed by the NCGC was adapted from the model developed by Bottomley and colleagues[213] and was validated by the GDG as a reasonable reflection of current clinical practice. The Markov model and how patients move through the pathway is illustrated in Figure 5. Key model assumptions (these are discussed in more detail in the full write-up in Appendix M):

- All hypothetical patients commence treatment with a given topical and experience one of two outcomes after 4 or 8 weeks:
  - response (defined as clearance/near clearance of their psoriasis)
  - no response (defined as something less than clearance/near clearance of their psoriasis).
- Patients who respond stop treatment and they either maintain response in the absence of treatment or they relapse.
  - Patients who relapse resume treatment with the same topical and again face a probability of responding or not responding.
- Patients who do not respond to a given topical after 8 weeks of treatment are assumed to return to their GP and receive a prescription for an alternative topical therapy.
- Patients can receive up to three different topical therapies before being referred by the GP to a specialist review in an outpatient dermatology clinic where second-line treatment options could be considered.
  - Some proportion of these referred patients will be kept on topical therapies, receive support and advice at the review consultation and be discharged back to their GP for long-term management.
  - The remaining proportion undergo a course of phototherapy:
    - If they respond to phototherapy they are then discharged to their GP for long-term management.
    - If they do not respond to phototherapy they continue to be managed by a specialist.

Movement between various health states is governed by transition probabilities, derived from the systematic review of clinical effectiveness data. Thirteen 4-week cycles were modelled, resulting in a 1-year time horizon for the analysis, with a half-cycle correction applied.

Figure 5: Markov model of treatment with topical therapy



Model inputs were based on the clinical effectiveness review undertaken for the guideline, other published data and expert opinion where required. These are described in full in the technical report in Appendix M. All model inputs and assumptions were validated by the GDG.

8.4.242 Results

This analysis found that, given a NICE willingness-to-pay threshold of £20,000 per QALY gained, the most cost-effective strategy is likely to be one of starting with twice daily potent corticosteroid and moving to concurrent potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening) and then twice daily coal tar. This strategy was also the least costly strategy among the 122 modelled. Base case results for non-dominated and non-extendedly dominated strategies are presented Table 69.

Results showed that starting with concurrent potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening) and switching to twice daily potent corticosteroid and then twice daily coal tar is £9 more costly over 1 year and only produces 0.0004 more QALYs than the least costly strategy mentioned above. This gives it an incremental cost-effectiveness ratio (ICER) of £23,250 which is just above the NICE £20,000 per QALY threshold.

The most effective strategy (once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate then twice daily potent corticosteroid then twice daily coal tar) costs an additional £192 per year compared to the next most costly non-dominated strategy (concurrent

steroid and vitamin D or vitamin D then twice daily potent steroid then twice daily coal tar), yet produces just 0.0011 additional QALYs for an ICER of over £174,000. Based on the results of this model, it appears that starting with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate , although most effective, is very unlikely to be cost-effective.

Table 69: Incremental analysis of base case results – psoriasis of trunk and limbs

Strategy (a)	Cost	Incremental Cost	Benefit (QALYs)	Incremental Benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	Probability most cost effective at £20k threshold (b)
PS BD - Concurrent - Coal Tar BD	£226.50		0.8487			22%
Concurrent - PS BD - Coal tar BD	£235.80	£9.30	0.8491	0.0004	£23,250	21%
TCF OD - PS BD - Coal Tar BD	£427.80	£192.00	0.8502	0.0011	£174,545	0%

(a) All sequences not presented here were ruled out through dominance (more costly and less effective than a strategy included in the table) or extended dominance (more costly and less effective than a mixture of two other strategies included in the table)

(b) Strategies not on the cost-effectiveness frontier but with high likelihood of being cost effective include PS BD – Concurrent – Vit D BD and Concurrent – PS BD – Vit D BD (optimal in 12% and 11% of simulations and ranked third and fourth in terms of NMB, respectively)

Results of the analysis showed that a strategy of using vehicle or emollient with no active agent only was the most costly and least effective, largely driven by the cost of referrals and specialist management for non-responders. Strategies that included once or twice daily vitamin D or vitamin D analogue were not cost-effective regardless of where they were included in the sequence. This is largely due to their relatively low rank in terms of effectiveness and their relatively high acquisition cost. Strategies that included dithranol were also all dominated, that is more costly and less effective than alternatives. Finally, strategies in which patients were referred after non-response to only 2 topicals were all dominated, thus not cost effective.

The probabilistic analysis indicates that there is a great deal of uncertainty as to which sequence is optimal (i.e. most cost effective). There appears to be very little difference between initial potent corticosteroid followed by concurrent potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening) and vice versa, with the difference in their net monetary benefits (NMB) being only £1 (£16,748 and £16,747 respectively) and both having a roughly equal probability of being optimal at a £20,000 willingness to pay threshold. Generally, it looks as though a strategy of starting with either potent corticosteroids or concurrent treatment with potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening) is most likely to be cost-effective, whereas starting with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate is very unlikely to be cost-effective.

A series of sensitivity analyses suggested that the conclusions from the base case are sensitive to changes in some parameters and/or assumptions.

Sensitivity analyses – Treatment effects

The network meta-analysis of topical therapies was performed for two response outcomes: investigator assessed global improvement (IAGI) and patient assessed global improvement (PAGI). The economic evaluation used the investigator assessed outcome in the base case, largely because

there was more data from the randomised evidence reported for this outcome. In a sensitivity analysis, treatment effects from the network meta-analysis of patient reported outcome was used.

Results of the analysis using patient reported outcomes indicates that starting treatment with once daily potent corticosteroids, moving on to the concurrent treatment if that fails and then trying twice daily vitamin D or vitamin D analogue is likely to be both the least costly and most cost-effective strategy given a threshold of £20,000 per QALY gained. Initial treatment with concurrent potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening) appears less cost-effective using patient reported outcomes than physician reported outcomes, unlikely to be cost-effective at thresholds less than £70,000. Once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate, first or second line in a sequence, still looks to generate additional benefits (QALYs), but at additional costs unlikely to be considered good value for NHS resource (ICERs upwards of £110,000 per QALY gained).

The base case network meta-analysis of physician/investigator assessed response used in the base case cost-effectiveness analysis included all RCTs that met the inclusion criteria for the clinical review of direct evidence. The review of direct evidence was quite focused and as such did not include evidence for every possible pair wise comparison. In a sensitivity analysis of the network meta-analysis and thus the cost-effectiveness analysis, additional studies were included. For details on the particulars of these sensitivity analyses and what effect they had on the estimated treatment effects, see Appendix K.

When treatment effects were based on all relevant RCT data, the results of the base case changed only slightly. Twice daily potent corticosteroid followed by concurrent steroid and vitamin D or vitamin D analogue(one applied in the morning and one in the evening) is still likely to be optimal for first and second line treatments. However, instead of twice daily coal representing the optimal third line topical, twice daily vitamin D or vitamin D analogue looks to be most cost-effective. This sensitivity analysis calls into question whether vitamin D or vitamin D analogue or coal tar represents the better third line treatment option.

Sensitivity analysis – Utility values

In the base case, the mean utility gain associated with achieving some level of improvement, but not clearance or near clearance was assumed to be 0.05. This value was based on a downward adjustment of a value used in a recent cost-utility analysis included in the health economic review. Bottomley and colleagues[213] modelled a utility gain of 0.07 for non-responders compared to baseline. To see what effect the GDG adjustment had on the results, the Bottomley figure (0.07) was used in a sensitivity analysis

Results indicate that the conclusion about cost-effectiveness changes very little using this more optimistic estimate of utility gain. The ICERs for all strategies increases relative to the base case; therefore, starting with concurrent treatment before twice daily potent corticosteroids is less likely to be cost-effective (ICER=£88,333 vs £23,250 in the base case). Similarly, the ICER for a strategy starting with combined product containing calcipotriol monohydrate and betamethasone dipropionate increased to over £787,000 compared to starting with concurrent treatment (£174,500 in the base case).

Sensitivity analysis – 4-week quantity of combined product containing calcipotriol monohydrate and betamethasone dipropionate

In the base case, hypothetical patients are assumed to use 134.0 g of combined product containing calcipotriol monohydrate and betamethasone dipropionate during 4 weeks of treatment. Bottomley and colleagues used a much lower value for this input (92.6 g), and we explored how the results of the NCGC analysis might change if this lower estimate was used. The cost of 92.6 g of combined

product containing calcipotriol monohydrate and betamethasone dipropionate was £61.27 (compared to £94.26 in the base case). The results of this sensitivity analysis showed that the ICER for combined product containing calcipotriol monohydrate and betamethasone dipropionate improved compared to the base case (£124,400 vs £174,545); however this is still well above the NICE cost-effectiveness threshold of £20,000 per additional QALY. Initial therapy with twice daily potent corticosteroid or concurrent vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening) is still more likely to be considered cost-effective.

Sensitivity analyses – Restricted comparators

The base case analysis put a several conditions on the way topicals could be sequenced (see Table 68 in section 8.4.2.1). These conditions did not restrict how potent corticosteroids were fit into treatment sequences other than that they could not appear in all three lines of treatment. This included their use as part of concurrent or combined treatment. The GDG expressed concern that these restrictions may not fully reflect the caution they would use in prescribing trials of potent corticosteroids, in that the BNF discourages continuous use of potent corticosteroids for more than 8 weeks at a time. The GDG was also concerned that the analysis did not fully capture the safety risks associated with the continuous or intermittent use of twice daily potent steroids. In a series of sensitivity analyses, various additional restrictions were placed on the treatment sequences.

In the first scenario, it was assumed that interventions that included potent corticosteroids could not be offered consecutively. For example, once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate could not be offered after treatment with once or twice daily potent corticosteroids, nor could twice daily potent corticosteroid follow once daily potent corticosteroid. Under this assumption, starting with twice daily corticosteroid, then trying twice daily vitamin D or vitamin D analogue and then using both potent corticosteroid and vitamin D or vitamin D analogue concurrently (one applied in the morning and one in the evening)would represent the best value for NHS resources given a £20,000 per QALY threshold. Starting with concurrent treatment would only be cost-effective at thresholds of greater than £33,000 and combined product containing calcipotriol monohydrate and betamethasone dipropionate would only be cost-effective at thresholds over £202,000.

In the second scenario, it was assumed that twice daily corticosteroid could not be prescribed as a first or second line topical therapy, but consecutive use of potent corticosteroids was permitted. Under this scenario, the optimal strategy was to start with concurrent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening), then try twice daily vitamin D or vitamin D analogue alone and finally twice daily potent corticosteroid only. This had an ICER of £18,000 per QALY gained compared to once daily potent corticosteroid followed by concurrent treatment and then twice daily coal tar. Strategies including combined product containing calcipotriol monohydrate and betamethasone dipropionate either as second or first line were not cost-effective unless the threshold was over £110,000 and £446,000, respectively.

A third scenario combined the first and second scenarios, such that twice daily potent corticosteroid could not be prescribed as first or second line treatment and no sequences could include consecutive lines of potent steroid containing strategies. Under these conditions, the same sequence as in scenario 2 is most cost-effective (concurrent – vit D BD – PS BD). Combined product containing calcipotriol monohydrate and betamethasone dipropionate replaces twice daily steroid in that sequence only if the threshold willingness to pay is £134,000 and replaces concurrent treatment in the same sequence if the threshold is £202,000.

In a fourth and final scenario, twice daily potent corticosteroid was removed entirely and no potent steroid containing products could be prescribed consecutively. Under this assumption, the most cost-effective sequence was initial concurrent treatment followed by twice daily vitamin D or vitamin D analogue alone and then twice daily coal tar. Combined product containing calcipotriol

monohydrate and betamethasone dipropionate replaces twice daily coal tar in that sequence at a threshold of over £47,000 and replaces concurrent treatment at a threshold of over £489,000.

Sensitivity analyses – downstream resource use and cost

Changes to the assumed probability of referral to secondary care and proportion offered phototherapy have no meaningful effect on the conclusions of the base case. The probability of referral to secondary care was varied downwards to 40% and upward to 80%. When referral occurred less often than in the base case, there was no change to the rank order of strategies, but the ICER for a strategy where combined product containing calcipotriol monohydrate and betamethasone dipropionate was used first instead of concurrent treatment increased to £200,000 per additional QALY. When referral occurred more often than in the base case, there was still no change in the rank order, but the ICER for combined product containing calcipotriol monohydrate and betamethasone dipropionate was slightly lower. If the probability of undergoing UVB phototherapy upon referral was higher than in the base case (50% vs 30%), then the ICER for combined product containing calcipotriol monohydrate and betamethasone dipropionate compared to concurrent treatment reduced slightly, but not enough to make it cost-effective. Finally, if instead of assuming patients are treated with UVB phototherapy, it is assumed they receive outpatient day care treatment with specialist supervised topical therapies, then the ICER for concurrent therapy before potent corticosteroids alone increases to over £30,000 per QALY and the ICER for initial combined product containing calcipotriol monohydrate and betamethasone dipropionate instead of concurrent therapy decreases to £155,000 per QALY.

If the time horizon is extended for 2 to 3 years and cumulatively more patients see a specialist and move on to UVB phototherapy, then initial treatment with concurrent vitamin D or vitamin D analogue and potent corticosteroids (one applied in the morning and one in the evening) becomes more cost-effective than starting with potent corticosteroids alone. When the time horizon is extended, combined product containing calcipotriol monohydrate and betamethasone dipropionate becomes more cost-effective compared to concurrent treatment (ICER = £118,000 at 2 years; ICER = £90,000 at 3 years), but is still very unlikely to be considered cost effective given the NICE willingness to pay threshold of £20,000 per QALY gained.

8.4.293 Interpretation and limitations

In assessing the relative cost-effectiveness of alternative topical therapies in patients with mild to moderate psoriasis limited evidence was available from the published economic literature. The evidence that was identified and included in the health economic review had potentially serious limitations and therefore the GDG considered it a priority to undertake original evaluation for the guideline in order to inform recommendations. This analysis showed that there were relatively small differences in terms of benefit between different topical sequences, but the differences in terms of cost were quite substantial. Based on the mean costs and benefits, the analysis suggests that initial treatment with potent corticosteroids followed by concurrent treatment with potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening) and followed then by twice daily coal tar therapy is likely to represent the most cost-effective sequence for implementation in primary care. Uncertainties in the analysis were explored through sensitivity analysis which showed that in some scenarios

- Once daily potent corticosteroid or concurrent treatment should come first in the sequence
- Twice daily vitamin D or vitamin D analogue should come second or third in the sequence, after concurrent treatment
- Combined product containing calcipotriol monohydrate and betamethasone dipropionate should be offered third in the sequence, after potent corticosteroids and concurrent treatment

Sequences starting with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate were slightly more effective than the same sequence starting with concurrent potent corticosteroid and vitamin D or vitamin D analogue (one applied in the morning and one in the evening); however, the very modest additional benefit (0.0011) would only be considered potentially cost-effective if willingness to pay thresholds were between £100,000 and £500,000 per QALY gained.

The analysis has several limitations which were considered carefully by the GDG. Firstly, the analysis evaluates treatment sequences even though the available trial data compares single topicals head to head without sequencing. In order to apply the treatment effects within the sequencing model, we assumed that treatment effects were independent. That is, we assumed the effectiveness of combined product containing calcipotriol monohydrate and betamethasone dipropionate as a second or third line topical was equal to its effectiveness as a first line agent and that this was true regardless of other topicals it may follow. The GDG did not believe this to be a significant limitation given that the patients included in the overwhelming majority of RCTs were reported to have psoriasis for longer than 5 years, during which the can be assumed to have previously tried, succeeded and/or failed various topical treatments.

The analysis only captured the efficacy of topicals and did not capture the costs or consequences of adverse events. Although the RCT evidence on adverse events was sparse, the GDG is conscious of the risks associated with the long-term use of potent and very potent corticosteroids. They carefully considered whether the added effect in terms of clearance was worth the potential risks of adverse effects.

The model was also focused on the induction of disease clearance as opposed to the maintenance of clearance. Trials focusing on maintenance were limited in number and inadequately reported for use in the economic model. In particular, there was uncertainty as to how maintenance treatments were applied in the trials and therefore incorporating such evidence and assumptions into the model was considered too difficult and unlikely to be valid.

The model also takes a relatively short time horizon considering that psoriasis is a chronic, long term condition for which patients may undergo treatment for many years of their lives. Frequency and severity of relapse, selection for and speed of onward referral, methods of self-management and long-term safety are all issues inadequately addressed in the evidence base and therefore translate into limitations of the economic analysis.

8.4.224 Comparison with published studies

The findings from the NCGC original economic analysis are quite different from the results of the most similar published study by Bottomley and colleagues[213]. Bottomley and colleagues found 8 weeks of once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate to dominate other modelled strategies including once and twice daily vitamin D or vitamin D analogue followed by potent corticosteroid, potent corticosteroid followed by vitamin D or vitamin D analogue and 8 weeks of concurrent treatment with vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening). Although the analysis appears to have been executed well, the estimates of effect and resource use had limitations which called the conclusions of the analysis into question.

The biggest differences in the results of the NCGC analysis presented here and the analysis undertaken by Bottomley has to do with the treatment effect sizes used. In their analysis, concurrent treatment was found to be very ineffective, with just 14.9% of patients responding with a PASI75 compared to the combined product containing calcipotriol monohydrate and betamethasone dipropionate to which 50.3% of patients responded (RR=3.38). The NCGC analysis showed a much small difference between these treatments, with 65.1% of patients responding to concurrent

treatment and 70.7% responding to The combined product containing calcipotriol monohydrate and betamethasone dipropionate (RR=1.09).

In addition, the estimate they used for quantity of topical used per 4-week treatment period was 92.6 g, compared to the estimate used in the NCGC analysis 134.0 g. Based on these estimates of resource use, the NCGC analysis assumes 4 weeks of the combined product containing calcipotriol monohydrate and betamethasone dipropionate costs £29.26 more than Bottomley and colleagues did. Furthermore, the difference between the combined product containing calcipotriol monohydrate and betamethasone dipropionate and concurrent treatment is different between the analyses. The additional cost of the combined product containing calcipotriol monohydrate and betamethasone dipropionate was £36.91 in Bottomley and more than twice that, £76.34, in the NCGC analysis. We performed a sensitivity analysis in which we assumed the same quantity of the combined product containing calcipotriol monohydrate and betamethasone dipropionate used by Bottomley and colleagues (i.e. 92.6 g, £61.27). The ICER for the combined product containing calcipotriol monohydrate and betamethasone dipropionate improved compared to the base case (£124,400 vs £174,545), but was still well above the NICE cost-effectiveness threshold of £20,000 per additional QALY.

The one thing that Bottomley and colleagues were able to capture that the NCGC analysis was not had to do with the potential disutilities associated with adverse events; however these inputs were not reported, were not included in their base case and, their impact on the results were not reported in full. The authors simply state that the influence of AEs 'had no impact on the results.'

8.4.13 Evidence statements

- One partially applicable study with potentially serious limitations found that short-contact dithranol may be more cost-effective than calcipotriol.
- One directly applicable study with potentially serious limitations found that a combined product containing calcipotriol monohydrate and betamethasone dipropionate administered once daily may be more cost effective than concurrent but separate treatment with vitamin D or vitamin D analogue and potent corticosteroids (one applied in the morning and one in the evening) and both vitamin D or vitamin D analogue alone (once daily and twice daily) and potent corticosteroids alone (once daily).
- One partially applicable study with potentially serious limitations found that six weeks of vitamin D or vitamin D analogue offered after a trial of potent corticosteroids is likely to be cost effective compared to four or six weeks of very potent corticosteroids offered after a trial of potent corticosteroids; however, it is less likely to be cost effective compared to two weeks of very potent corticosteroids.
- One partially applicable study with potentially serious limitations found that vitamin D or vitamin D analogue offered after failure of potent corticosteroid is likely to be cost effective compared to continued treatment with alternative potent corticosteroids.
- New economic analysis from a current UK NHS and PSS perspective comparing 122 different sequences of topical therapies found twice daily potent corticosteroids or concurrent treatment (one in the morning and one in the evening) with potent corticosteroid and vitamin D or vitamin D analogue to be the most cost-effective options for the first and second line treatment of patients with mild to moderate chronic plaque psoriasis. This conclusion was robust to the majority of sensitivity analyses undertaken.
    - The base case and sensitivity analyses showed that the choice of third line treatment in a given sequence was highly uncertain. Depending upon the data used and assumptions made, third line treatment with twice daily coal tar, twice daily vitamin D or vitamin D analogue or once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate was likely to be most cost effective.

8.5 Recommendations and link to evidence

General recommendations on topical therapy	**25.Offer people with psoriasis topical therapy as first-line treatment and escalate to second-line treatment (that is, phototherapy or systemic non-biological therapy) or third-line treatment (systemic biological therapy) if psoriasis is extensive and/or severe.** **26.Offer practical support and advice about the use and application of topical treatments. Advice should be provided by healthcare professionals who are trained and competent in the use of topical therapies. Support people to adhere to treatment in line with 'Medicines adherence' (NICE clinical guideline 76)** **27.Be aware that continuous use of potent or very potent corticosteroids may cause:** • **irreversible skin atrophy and striae** • **psoriasis to become unstable** • **systemic side effects when applied continuously to extensive psoriasis.** **Explain the risks of these side effects to people undergoing treatment and discuss how to avoid them.** **28. When offering a corticosteroid for topical treatment choose a low-cost preparation.** **29.Do not use potent or very potent corticosteroids on the face or flexures, including genital sites.** **30.Do not use very potent corticosteroids continuously at any site for longer than 4 weeks.** **31. Do not use potent corticosteroids continuously at any site for longer than 8 weeks.** **32. When offering topical agents take into account patient preference, cosmetic acceptability, practical aspects of application and the site(s) and extent of psoriasis to be treated. Discuss the variety of formulations available and use:** • **cream or lotion for widespread psoriasis** • **lotion, solution or gel for the scalp or hair-bearing areas** • **ointment to treat areas with thick adherent scale.** **Be aware that topical treatment alone may not provide satisfactory disease control, especially in people with severe psoriasis.** **33.If a person with psoriasis has a physical disability or visual impairment and needs topical therapy, offer advice and practical**

	support that take into account the person's individual needs. **34. Arrange a review appointment at 4 weeks after starting a new topical treatment strategy to evaluate tolerability, toxicity and initial response to treatment.** **35. Discuss with people whose psoriasis is responding to topical treatment:** • **the importance of continuing treatment until a satisfactory outcome is achieved (for example clear or nearly clear) or up to the recommended maximum treatment period for corticosteroids (see sections 8.5 and 8.12)** • **that relapse occurs in most people after treatment is stopped** • **that topical treatments can be used as and when required to maintain satisfactory disease control.** **36. Offer people with psoriasis a supply of their topical treatment to keep at home for the self-management of their condition.** **37. In people whose psoriasis has not responded satisfactorily to a topical treatment strategy, before changing to an alternative treatment:** • **discuss with the person whether they have any difficulties with application, cosmetic acceptability or tolerability and where relevant offer an alternative formulation** • **consider other possible reasons for non-adherence in line with 'Medicines adherence' (NICE clinical guideline 76).**
Recommendations on topical therapy for psoriasis of the trunk and limb	**38. Offer a potent corticosteroid applied once daily plus vitamin D or a vitamin D analogue applied once daily (applied separately, for example one agent applied in the morning and the other in the evening) for a maximum period of 8 weeks as initial treatment for psoriasis of the trunk or limbs in adults.** **39. If once-daily application of a potent corticosteroid plus vitamin D or a vitamin D analogue does not result in clearance, near clearance or satisfactory control of psoriasis of the trunk or limbs in adults after 8 weeks, offer vitamin D or a vitamin D analogue alone applied twice daily.** **40. If twice-daily application of vitamin D or a vitamin D analogue does not result in clearance, near clearance or satisfactory control of trunk or limb psoriasis in adults by 8–12 weeks offer either:** • **a potent corticosteroid applied twice daily for up to 8 weeks or** • **a coal tar preparation applied once or twice daily.** **41. If a twice-daily potent corticosteroid or coal tar preparation cannot be used and a once-daily preparation would improve adherence, offer a combined product containing calcipotriol**

	monohydrate and betamethasone dipropionate applied once daily for up to 8 weeks. **42. Offer treatment with very potent corticosteroids in adults with trunk or limb psoriasis only:** • **in specialist settings under careful supervision** • **when other topical treatment strategies have failed** • **for a maximum period of 4 weeks.** **43. Consider short-contact dithranol for treatment-resistant psoriasis of the trunk or limbs and either:** • **give educational support for self-use or** • **ensure treatment is given in a day-care setting.** **44. Offer a review at least annually to people with trunk or limb psoriasis who are using a potent or very potent corticosteroid (either as monotherapy or in combined preparations) to assess for the presence of steroid atrophy and other adverse effects.** **45. For children and young people with trunk or limb psoriasis consider either:** • **calcipotriol applied once daily or** • **a potent corticosteroid applied once daily.** **Review treatment 2 weeks after starting treatment.**
Future research recommendations	**11. What are the risks of 'real life' long term corticosteroid use in people with psoriasis (for example steroid atrophy, unstable psoriasis), are there any individuals at particular risk, and what strategies can be used to modify or avoid these risks?** **12. How should topical therapies be used to maintain disease control safely and effectively?**
Relative values of different outcomes	The relative values of the different outcomes for scalp, face and flexural sites are the same as for trunk and limbs. • Clear/nearly clear (investigator) • Clear/nearly clear (patient) • % change in PASI • Duration of remission • Withdrawal due to toxicity • Withdrawal due to lack of efficacy • Skin atrophy Based on the results from the pairwise and network meta-analyses and the health economic model the GDG decided to recommend potent corticosteroids as the first topical intervention, followed by very potent steroids if this failed, as this was the most cost-effective option based

	on the investigator and patient assessment of achieving clear or nearly clear status. There was no clinically significant difference between most interventions in terms of withdrawal due to toxicity and skin atrophy as the absolute numbers were low and clear evidence regarding duration of remission was lacking. It was also noted that the pair-wise comparison of a combined product containing calcipotriol monohydrate and betamethasone dipropionate compared to potent steroid alone (applied once daily for the scalp) did not show a clinically significant difference in efficacy, unlike for this comparison for treatment of the trunk and/or limbs.
Trade off between clinical benefits and harms	As with the use of corticosteroids on the trunk and limbs, the efficacy, time to clearance and cosmetic acceptability were felt to outweigh the potential risks of corticosteroids for treatment of the scalp. The GDG discussed the data showing that of those who respond by 8 weeks to potent corticosteroid treatment, approximately 84% had done so by 4 weeks. Therefore, it was agreed to consider different formulations and topical agents to remove scale if treatment had not been successful by 4 weeks. The GDG noted that, unlike at the trunk and limbs, from the scalp data there was a non-significant trend towards once daily application of a given topical to be more effective than twice daily application for all agents except very potent corticosteroids. This was in line with clinical experience that twice daily scalp treatments are not favoured by patients often resulting in poor adherence. Therefore, to optimise outcomes once daily application was recommended where possible as well as emphasising the importance of using the correct formulation and removal of adherent scale, which is particularly important when treating scalp psoriasis. When considering clinically appropriate sequences of treatment for scalp psoriasis the GDG agreed that starting with a very potent corticosteroid as the first topical intervention would be an inappropriately aggressive strategy. The GDG were more cautious when considering this trade off in favour of corticosteroids at face and flexural sites as risks of skin atrophy are higher. The GDG considered that only mild, or if necessary moderate potency corticosteroid could be justified. Calcineurin inhibitors whilst effective are unlicensed for psoriasis. The GDG considered that given the paucity of other options, the impact psoriasis has on these sites and also that these agents are licensed and widely used in eczema, they could be recommended following specialist advice.
Economic considerations	The GDG relied on a variety of sources in their consideration of the costs and benefits of alternative topical therapies in the treatment of patients with scalp psoriasis. Limited evidence, both in terms of quantity and quality, was identified in the published literature. One study showed that starting with twice daily betamethasone valerate (potent corticosteroid) followed by concurrent treatment (am/pm) with betamethasone dipropionate (potent corticosteroid) and calcipotriol (vitamin D analogue) and then once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate to be the most cost-effective treatment sequence. Due to limitations of the

study, the GDG remained uncertain about the robustness of these conclusions.

Original decision modelling was undertaken for the guideline and showed that there were relatively small differences in terms of benefit between different topical sequences for scalp psoriasis, but large differences in terms of cost. Based on the mean costs and benefits of 169 compared sequences, the analysis found that initial treatment with twice daily very potent corticosteroids is likely to offer the best value for NHS resource. The GDG was concerned that twice daily very potent corticosteroid, although most effective and cost-effective, is quite an aggressive initial strategy and carries greater risk of steroid-related adverse events, which were not captured by the model. Furthermore, the GDG noted strong patient preference for once daily applications due to the messiness, inconvenience and cosmetic acceptability of topicals applied to the scalp. Therefore the GDG chose not to recommend twice daily very potent steroids as either the first or second-line treatment. It was considered appropriate as third-line treatment, as the number of patients exposed to the risks would be fewer but the need for efficacy more urgent.

Of the remaining strategies, the two most cost-effective strategy were:

- 1st line – once daily potent corticosteroid; 2nd line - once daily vitamin D or vitamin D analogue ; 3rd line – twice daily very potent corticosteroid
- 1st line – once daily potent corticosteroid; 2nd line - once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate; 3rd line – twice daily very potent corticosteroid

Where a less aggressive 3rd-line treatment is required, once daily very potent steroid or coal tar are alternatives, which are cost-effective compared to referral.

The analysis also considered the cost-effectiveness of coal tar polytherapy (Capasal® shampoo) relative to other topicals in the treatment of scalp psoriasis. Coal tar based shampoo was only slightly more effective that placebo/vehicle scalp solution and far less effective than other topicals. In the model, this meant that more patients ended up failing treatment in primary care and being referred onward for specialist consultations and treatments, thus making the true costs to the NHS of treatment with coal tar shampoos much higher than the acquisition cost alone. The GDG was aware that coal tar based shampoos are regularly prescribed in primary care for treatment of scalp psoriasis and agreed that based on the evidence of clinical and cost-effectiveness that they are not optimal for the treatment of scalp psoriasis. In order to ensure more efficient use of NHS resources, they considered it important to discourage GPs from using this particular treatment modality.

No economic evidence was available to inform the GDG on the relative cost-effectiveness of topicals in the treatment of psoriasis at sites such as the face and flexures. Given the cost-effectiveness of corticosteroids

	in the treatment of psoriasis of the trunk, limbs and scalp, the GDG concluded that corticosteroids were likely to represent good value for money in the treatment of psoriasis of the face and flexures, if side-effects are manageable. However, they noted the substantial risk of skin atrophy associated with corticosteroid use at these sites, and thus concluded that neither potent nor very potent corticosteroids were safe or appropriate. In the absence of clinical and economic evidence, the GDG relied on their clinical experience with mild and moderate potency corticosteroids. They concluded that their low acquisition cost was very likely to be justified by the benefits gained compared to alternatives. Calcineurin inhibitors are more costly than moderate potency corticosteroids and are not licensed for the treatment of psoriasis. The GDG considered that they may represent good value for NHS resources if continuous treatment is required (and thus the risk of steroid-associated side effects is higher) or if moderate potency corticosteroids fail to bring about the desired level of response.
Quality of evidence	All studies The majority of the data on withdrawals (except withdrawals due to lack of efficacy for the placebo comparisons) and skin atrophy across all comparisons showed low event rates that gave very imprecise relative estimates, but in absolute terms demonstrated precise evidence of no clinically relevant difference between the interventions because the numbers involved were so low. Even in cases where there was a statistically significant difference in the interventions, such as withdrawals due to adverse events in the comparison of potent corticosteroids and placebo, in absolute terms there was no clinically significant difference between the interventions. The study limitations regarding steroid atrophy discussed in relation to trunk and limbs (see 7.4.4) also apply to high impact and difficult to treat sites. There was a lack of information regarding the duration of remission/time-to-relapse, which was only reported in 3 studies (Poulin 2010, Klaber 1994 and Kragballe 2009). While there was an overall trend that the relapse rate was higher following use of preparations including potent steroids compared with vitamin D or vitamin D analogues the different definitions of relapse and time-points of assessment made it difficult to assimilate the data. **Scalp psoriasis** Vitamin D and vitamin D analogues vs placebo: There was heterogeneity between two studies (Jemec 2008 and Green 1994) included in the comparison of vitamin D and vitamin D analogues vs. placebo for scalp psoriasis for the outcome of investigator's assessment of achieving clear or nearly clear which wasn't explained by pre-defined subgroups but may have been due to a higher risk of bias in the Green 1994 study. Nevertheless, both studies suggest that vitamin D and vitamin D analogues are clinically beneficial in terms of achieving clearance or near clearance compared with placebo treatment.

Potent corticosteroid vs placebo: One study (Franz 1999) investigating potent corticosteroid vs. placebo on the scalp included two experimental arms with different formulations of active treatment. Although it was not within the review protocol to investigate differences in formulation the GDG noted that a statistically significant difference was demonstrated between the foam and lotion formulations of betamethasone valerate (foam = 72% response, lotion = 47% response on investigator's assessment; results for the patient's assessment were similar).

Very potent corticosteroid vs placebo: The studies (Franz 2000, Olsen 1991, Jarratt 2004 and Sofen 2011) for scalp very potent corticosteroid vs. placebo ranged from two to four weeks duration, which may be too short a timeframe to detect skin atrophy. As with potent steroid, foam formulations were more effective than lotion formulations; however the difference was not statistically significant for very potent corticosteroids. One study (Poulin 2010) looked at maintenance of response using very potent steroid vs placebo for up to 6 months but was noted to be of very low quality because once daily clobetasol propionate was permitted for up to 4 weeks if relapse occurred in clobetasol or vehicle group. During the whole study, clobetasol propionate was applied for 79.3 days in the clobetasol propionate group and 59.5 days in the vehicle group.

Potent corticosteroids vs vitamin D or vitamin D analogue: There was unexplained heterogeneity between the studies (Jemec 2008, van der Kerkhof 2009 and Klaber 2004) for the efficacy outcomes, but betamethasone dipropionate was clinically beneficial compared to vitamin D or vitamin D analogue treatment.

Very potent steroids compared with other active treatments: One study (Reygagne) compared very potent corticosteroid with vitamin D or vitamin D analogue treatment. The skin atrophy treatment effect was unclear because some atrophy was present at baseline. The GDG noted that there were no direct data comparing very potent steroids with other active treatments. However, from the network meta-analysis twice daily very potent corticosteroids were likely to be the most effective treatment. However, once daily potent corticosteroid or combined product containing potent steroid and vitamin D analogue (calcipotriol monohydrate and betamethasone dipropionate) may be more effective than once daily very potent corticosteroid.

Combined product containing calcipotriol monohydrate and betamethasone dipropionate vs. vitamin D or vitamin D analogue alone: There was heterogeneity between the 3 studies (Kragballe2009, Jemec 2008 and van de Kerkhof 2009) for the outcome of patient's assessment of scalp clearance comparing a combined product containing calcipotriol monohydrate and betamethasone dipropionate vs. vitamin D or vitamin D analogue alone. This may have been because Kragballe 2009 used a gel formulation of the combined preparation and a solution of vitamin D analogue, so the combination formulation may have been more effective than the vitamin D analogue comparator formulation. All 3 studies suggest that a combined product is clinically

	beneficial in terms of achieving clearance or near clearance compared with vitamin D or vitamin D analogue treatment alone. Coal tar (shampoo): The GDG commented that the 4-8 week follow-up in the studies (Griffiths 2006A and McKinnon 2000) assessing coal tar to treat scalp psoriasis was too short term to be able to draw any conclusions about the time to maximum effect. It is known from the trunk and limb data that coal tar takes a long time to act. Relapse rate is very low so coal tar probably does have a role in some patients. In relation to different formulations, the GDG agreed that blinding was difficult especially with regard to tar and dithranol. The MacKinnon study was not felt to reflect clinical practice as coal tar shampoos are usually used as an adjunct rather than monotherapy. **Face and flexural (including genital) psoriasis** Overall there are little data for psoriasis at the face and flexural sites, and no data for corticosteroids at these sites. Use of mild to moderate corticosteroids for face and flexural disease is accepted as standard practice and the lack of trial data of sufficient quality to be included in the review is disappointing but may reflect the historical usage. Therefore, based on clinical experience, the GDG agreed to make a recommendation for their use. Regarding the graphical data for time-to-maximum effect with tacrolimus the findings of the Lebwohl and Liao studies for improvement are conflicting. The Lebwohl study found that the number or people improving after 29 days treatment with tacrolimus was minimal. The Liao study found though that patients with clear / almost clear psoriasis increased by 20% between four and six weeks of treatment. The GDG noted that in the Lebwohl study 0.1% tacrolimus was used compared with 0.03% tacrolimus in the Liao study. Therefore, the differences were thought to be explained by the lower strength formulation taking longer to act. **Scalp, face and flexural (including genital) psoriasis in children** The GDG commented on the lack of evidence for the treatment of children with psoriasis at difficult to treat sites; although two studies (Jarratt and Reygagne) included ages ≥12 the mean age in both was over 45 years. The GDG agreed that the recommendations for adults could be extrapolated to children and young people provided health care professionals also consulted the relevant SPC and BNF sections.
Other considerations	The GDG noted there were no studies that addressed maintenance. As with trunk and limbs, an as-needed approach to use of topicals was appropriate. The point at which treatment should be reinstituted is based on patient need. Return of scale was felt to be significant by patient members of the group. **Scalp psoriasis** It is difficult to assess skin atrophy on the scalp.

Use of corticosteroid on the scalp can be associated with inadvertent application to the face with consequent risk of skin atrophy, facial acne. Therefore careful application is important.

A post hoc subgroup analysis based on ethnicity (type V and VI skin) for the outcome of investigator's assessment of clear/nearly in the Tyring 2010 study found no significant difference between the subgroups when comparing a combined calcipotriol monohydrate and betamethasone dipropionate scalp formulation (gel) vs. placebo. However, post-hoc analyses are intrinsically at high risk of bias and the GDG noted that the severity of psoriasis can be underestimated in people with type V and VI skin.

Patient preference is an important factor in choosing a formulation to treat scalp psoriasis. The difference in cost of the formulations is small.

The majority of the data on withdrawals (except withdrawals due to lack of efficacy for the placebo comparisons) and skin atrophy across all comparisons showed low event rates that gave very imprecise relative estimates, but in absolute terms demonstrated precise evidence of no clinically relevant difference between the interventions because the numbers involved were so low. Even in cases where there was a statistically significant difference in the interventions, such as withdrawals due to adverse events in the comparison of potent corticosteroids and placebo, in absolute terms there was no clinically significant difference between the interventions. The limitations to the studies in relation to steroid atrophy discussed in the trunk and limbs section also apply to high impact and difficult to treat and high impact sites (see 7.4.4 for trunk and limbs).

The GDG felt that offering very potent corticosteroids first line would not be appropriate for scalp psoriasis. The GDG were mindful that the treatment is for long term use and relapse rates are higher with very potent steroids. Even use of potent steroid for scalp psoriasis in primary care would be a change in clinical practice. The GDG noted that the most of the evidence related to people with moderate or severe psoriasis; many people may present for treatment with scaling in the scalp alone and that this may be labelled 'scalp psoriasis' and treatment with very potent corticosteroids would not be appropriate. In these individuals coal tar shampoos may be appropriate.

From GDG experience, removing scale on the scalp before applying active treatment improves the efficacy of active treatment.

Face and flexures (including genitals)

Calcineurin inhibitors are not prescribed for psoriasis in primary care as they are not licensed to treat psoriasis; however they are licensed and widely used in eczema.

The GDG felt that intermittent short-term use of mild or moderately potent corticosteroids could be recommended in primary care but only for short-term use; use of topical calcineurin inhibitors should be on specialist advice given that these agents are unlicensed.

	The evidence suggested that for all interventions some level of response should be achieved by 4 weeks in those who are likely to gain benefit; therefore, the GDG agreed that it would be appropriate to review at 4 weeks to assess response to treatment. Additionally, for calcineurin inhibitors, the maximum response appears to be reached by 4 weeks so this was recommended as the treatment duration for this intervention. Non-concordance should be considered if there is no response to treatment in line with the NICE guideline on Medicines Adherence (CG76)[222]

8.6 Topical therapies for high impact or difficult sites

8.6.1 Methodological introduction

A literature search was conducted for RCTs or systematic reviews that compared the efficacy and safety of topical vitamin D and vitamin D analogues, mild to very potent corticosteroids, combined vitamin D or vitamin D analogue and potent corticosteroid or concurrent vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening), pimecrolimus, tacrolimus, tar, dithranol and retinoids in people with psoriasis at high impact and difficult to treat sites for the induction or maintenance of remission. The sites included were scalp, face and flexures (including genitals), which would be considered separately if stratified data were available.

No time limit was placed on the literature search and there were no limitations on duration of follow-up. However, indirect populations were excluded and the sample size had to be at least 25 participants in each arm.

The comparisons considered were any of the topical therapies compared with each other or with placebo/vehicle, while studies only comparing different dosages or formulations of the same intervention were excluded. Similarly, studies comparing interventions within the classes of either vitamin D or vitamin D analogues or corticosteroids were excluded (unless the comparison is for frequency of administration e.g., once or twice daily dosing). This is because we assume a class effect for these agents and so data on all vitamin D or vitamin D analogues was pooled into one analysis as was data on any potent corticosteroids and on very potent corticosteroids, unless heterogeneity was found.

The outcomes considered were:

- Clear/nearly clear or marked improvement (at least 75% improvement) on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)
- Clear/nearly clear or marked improvement (at least 75% improvement) on Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment
- Percentage change in PASI
- Change in DLQI
- Duration of remission
- Time-to-remission or time-to-maximum effect based on IAGI, PGA or total severity score (to address part ii of the question)*

- Withdrawal due to toxicity
- Withdrawal due to lack of efficacy
- Skin atrophy

Time-to-remission or time-to-maximum effect, absolute time-to-effect data or data from multiple time points in one study were reported as the first preference. Graphical data were only reported for interventions where such data were unavailable, or for long-term data not otherwise available. Additionally, data on IAGI, PGA or PAGI were reported in preference to TSS where available.

Twenty one RCTs[223-243] were found that addressed the question and were included in the review:

- 18 of these studies[225-237,239-243] addressed scalp psoriasis
- One study[223] addressed flexural psoriasis alone
- Two studies[224,238] addressed both face and flexural psoriasis
- Two studies[241;231] assessed long-term/maintenance treatment
- No studies were available to address the use of topical treatments at high-impact or difficult to treat sites in children

A published Cochrane Review[210] was available but was in the process of being updated by the Cochrane Review Group (and anticipated publication was outside of the development period of this guideline). The NCGC was unable to update the original Cochrane Review owing to differences in the outcomes required to feed in to a novel NCGC health economics model. The Cochrane review was used for NCGC cross referencing purposes and close collaboration between the Cochrane Review Group and NCGC meant that literature search strategies / protocols were shared. The Cochrane literature search was re-run and updated to include papers to the present day. Additionally, it was possible to use some of the data extracted on study characteristics and the withdrawal outcomes from the Cochrane Review. Please see the 'acknowledgement' section of this guideline.

The included studies differed in terms of the disease severity stated as an inclusion criterion as well as the treatment duration (see Table 70). The potential limitation of studies comparing interventions that act over different periods were noted(e.g., the faster acting clobetasol propionate and the slower acting calcipotriol), especially if the treatment duration chosen for the trial does not permit the maximum effect of the slower acting intervention to be observed.

Table 70: Disease severity inclusion criteria and treatment duration

Reference ID	Disease severity	Active intervention(s)	Maximum treatment duration
Scalp			
BUCKLEY 2008	Inclusion criteria: Involving >10% of the scalp surface area; mild to very severe disease according to PGA. Mean baseline TSS: 6.8 (range 0-12)	1. Calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g gel OD 2. Betamethasone dipropionate 0.5 mg/g gel OD	8 weeks
FRANZ 1999	Inclusion criteria: Moderate to severe scalp psoriasis (each of erythema, scaling and plaque thickness ≥ 2); scalp involvement ≥10%	1. Betamethasone valerate foam (0.1%) 2. Betamethasone valerate lotion (0.1%)	28 days
FRANZ 2000	Inclusion criteria: Moderate to severe scalp psoriasis (each of erythema, scaling and plaque thickness ≥ 2); scalp involvement ≥10%	1. Clobetasol propionate foam, 0.05% 2. Clobetasol propionate solution, 0.05%	2 weeks (plus 2 weeks post-treatment observation)

Reference ID	Disease severity	Active intervention(s)	Maximum treatment duration
GREEN 1994	Inclusion criteria: Mild to moderate scalp psoriasis Mean baseline TSS: 6.7 (range 0-12)	1. Calcipotriol solution, 50µg/ml BD	4 weeks
GRIFFITHS2006A	Inclusion criteria: Moderate-to-severe scalp psoriasis (affecting at least 15% of scalp area) Mean baseline TSS: 6.2 (range 0-9)	1. Clobetasol propionate shampoo 0.05% OD 2. Tar blend shampoo (arachis oil extract of coal tar 0.3% cade oil 0.3%, coal tar solution 0.1%, oleyl alcohol 1%, tar 0.3%) twice weekly	4 weeks
JARRATT 2004	Inclusion criteria: Moderate to severe scalp psoriasis (global severity score ≥ 3) Mean baseline TSS: 6.6 (range 0-9)	1. Clobetasol propionate shampoo, 0.05% OD	4 weeks (plus 2 week treatment-free follow-up)
JEMEC 2008	Inclusion criteria: Involving >10% of the scalp surface area; mild to very severe disease according to PGA. Mean baseline total severity score: 6.8 (range 0-12)	1. Calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g gel OD 2. Betamethasone dipropionate 0.5 mg/g gel OD 3. Calcipotriol 50 µg/g gel OD	8 weeks
JEMEC 2011	Inclusion criteria: Involving >10% of the scalp surface area; mild to very severe disease according to PGA. Mean baseline TSS: 6.8 (range 0-12)	1. Calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g gel OD 2. Betamethasone dipropionate 0.5 mg/g gel OD 3. Calcipotriol 50 µg/g gel OD	8 weeks
KLABER 1994	Inclusion criteria: Mild-to-moderate scalp psoriasis Mean baseline TSS: 6.5 (range 0-12)	1. Calcipotriol solution (50 µg/ml) BD 2. Betamethasone 17-valerate solution (1 mg/ml) BD	4 weeks (plus 4 week observation period for responders)
KRAGBALLE 2009	Inclusion criteria: Involving >10% of total scalp area; investigator's global assessment of disease at least "moderate" Mean baseline score not reported	1. Calcipotriol 50 µg/g + betamethasone 0.5mg/g gel OD 2. Calcipotriol scalp solution BD	8 weeks (+2 week off-treatment observation phase)
LUGER 2008	Inclusion criteria: Involving >10% of total scalp area; investigator's global assessment of disease at least "moderate" Mean baseline disease severity not stated	1. Calcipotriol 50 µg/g + betamethasone 0.5mg/g gel OD when required 2. Calcipotriol scalp gel OD when required	52 weeks
MCKINNON 2000	Inclusion criteria: Mild or moderate scalp psoriasis Mean baseline TSS: 5.1 (range 0-12)	1. Calcipotriol solution, 50 µg/g BD 2. Coal tar 1%, coconut oil 1%, salicylic acid 0.5% shampoo OD	8 weeks (plus 16 weeks for those who received calcipotriol and showed at least slight improvement)
OLSEN 1991	Inclusion criteria: Moderate to severe scalp psoriasis (TSS (0 to 9) ≥ 6)	1. Clobetasol propionate 0.05% scalp solution	2 weeks (plus 1 week post treatment observation)

Reference ID	Disease severity	Active intervention(s)	Maximum treatment duration
POULIN 2010	Inclusion criteria: Moderate scalp psoriasis (global severity score 3/5) Mean baseline severity not reported	1. Clobetasol propionate shampoo 0.05% twice weekly	Initial treatment phase (up to 4 weeks); then if clear, very mild or mild randomised to *maintenance* phase up to 6 months
REYGAGNE 2005	Inclusion criteria: Moderate-to-severe scalp psoriasis (GSS at least 3/5 and affected area at least 2 cm^2 of scalp) Mean baseline GSS: 3.5 (range 0-5) Mean baseline % scalp coverage: 45%	1. Clobetasol propionate shampoo 0.05% OD 2. Calcipotriol solution 0.005% BD	4 weeks
SOFEN 2011	Inclusion criteria: Moderate-to-severe scalp psoriasis (GSS at least 3/5)	1. Clobetasol propionate spray 0.05%	4 weeks
TYRING 2010	Inclusion criteria: Involving >10% of total scalp area; investigator's global assessment of disease at least "moderate" Mean baseline TSS: 6.3 (range 0-12)	1. Calcipotriol 50 µg/g + betamethasone 0.5mg/g gel OD	8 weeks (+2 week off-treatment observation phase)
VANDEKERKHOF 2009	Inclusion criteria: Involving >10% of the scalp surface area; mild to very severe disease according to PGA. Mean baseline TSS: 6.8 (range 0-15)	1. Calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g gel OD 2. Betamethasone dipropionate 0.5 mg/g gel OD 3. Calcipotriol 50 µg/g gel OD	8 weeks
Face and flexures (including genitals)			
GRIBETZ 2004	Inclusion criteria: Moderate to severe inverse psoriasis affecting axillae, inguinal, inframammary or gluteal cleft regions; PGA ≥ 3; erythema ≥2 Mean baseline TSS: 5.34 (range 0-9)	1. Pimecrolimus 1% cream BD	8 weeks
LEBWOHL 2004	Inclusion criteria: Chronic plaque psoriasis affecting intertriginous and facial skin; target lesion of moderate erythema and TSS (0 to 12) ≥4 Mean baseline severity score: 3 (6-point scale)	1. 0.1% tacrolimus ointment BD	8 weeks
LIAO 2007	Inclusion criteria: Chronic plaque psoriasis affecting the face and/or gentiofemoral area Mean baseline TSS: 6.2 (range 0-12)	1. Calcitriol 3 µg/g ointment BD 2. Tacrolimus 0.3 mg/g ointment BD	6 weeks

8.7 Topical therapies for high impact or difficult to treat sites: scalp psoriasis

8.7.1 Vitamin D or vitamin D analogue vs. placebo

8.7.1.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogues	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol OD (follow-up 4-8 weeks)											
2 Jemec 2008 Green 1994	randomised trials	very serious[a]	serious[b]	no serious indirectness	serious[c]	none	115/297 (38.7%)	35/160 (21.9%)	RR 2.12 (1.01 to 4.48)	245 more per 1000 (from 2 more to 761 more)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) - Calcipotriol OD (follow-up 8 weeks)											
1 Jemec 2008	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	104/272 (38.2%)	28/136 (20.6%)	RR 1.86 (1.29 to 2.67)	177 more per 1000 (from 60 more to 344 more)	⊕⊕⊕O MODERATE
Withdrawals due to adverse events - Calcipotriol OD (follow-up 4-8 weeks)											
2 Jemec 2008 Green 1994	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	21/260 (8.1%)	7/135 (5.2%)	RR 1.44 (0.65 to 3.21)	23 more per 1000 (from 18 fewer to 115 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy - Calcipotriol OD (follow-up 4-8 weeks)											
2 Jemec 2008 Green 1994	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	serious[g]	none	19/258 (7.4%)	18/146 (12.3%)	RR 0.57 (0.31 to 1.06)	53 fewer per 1000 (from 85 fewer to 7 more)	⊕⊕OO LOW

(a) 2/2 unclear allocation concealment; 1/2 high drop-out rate in both groups (21.0% of calcipotriol group and 22.1% of placebo); 1/2 unclear baseline comparability
(b) Significant heterogeneity was present (I^2 = 59%) that could not be explained in a clinically meaningful way by any of the pre-defined subgroups
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(d) Unclear allocation concealment and high drop-out rate in both groups (21.0% of calcipotriol group and 22.1% of placebo)
(e) Unclear allocation concealment and high drop-out rate in both groups (21.0% of calcipotriol group and 22.1% of placebo) in the trial weighted 94.8%
(f) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(g) Unclear allocation concealment and high drop-out rate in both groups (21.0% of calcipotriol group and 22.1% of placebo) in the trial weighted 89.3%
(h) Confidence interval ranges from clinically important effect to no effect

8.7.12 Evidence statements

In people with scalp psoriasis, topical calcipotriol once daily was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 4-8 weeks [2 studies; 457 participants; very low quality evidence][229,240]
- Patient's assessment (clear/nearly clear) at 8 weeks [1 study; 408 participants; moderate quality evidence][229]

In people with scalp psoriasis, there was no statistically significant difference between topical calcipotriol once daily and placebo for:

- Withdrawal due to adverse events at 4-8 weeks [2 studies; 395 participants; very low quality evidence][229,240]
- Withdrawal due to lack of efficacy at 4-8 weeks [2 studies; 404 participants; low quality evidence][229,240]

8.7.21 Heterogeneity

For the outcome of investigators assessment of achieving clear/nearly clear status moderate heterogeneity was present between the results for the two studies[229,240]. This may have been partly a result of the small size of one of the studies[240], but there were also other differences in the trials:

- One study[240] had a treatment duration of 4 weeks and used a calcipotriol solution, while the other[229] had a treatment duration of 8 weeks and used the gel formulation. However, the results have not been separated as these differences were thought not to be a clinically feasible explanation for the inconsistency. The large effect estimate may have been caused by high risk of bias as this study had a small sample size and baseline demographics were not reported in this study. Nevertheless, both studies suggest that vitamin D or vitamin D analogues are clinically beneficial in terms of achieving clearance or near clearance compared with placebo treatment.

8.7.13 Potent corticosteroid vs. placebo

8.7.3.21 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid (potent)	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											
2 Jemec 2008 Franz 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	424/671 (63.2%)	43/193 (22.3%)	RR 2.81 (2.14 to 3.68)	403 more per 1000 (from 254 more to 597 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) – betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											
2 Jemec 2008 Franz 1999	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	419/671 (62.4%)	38/193 (19.7%)	RR 3.15 (2.35 to 4.21)	423 more per 1000 (from 266 more to 632 more)	⊕⊕⊕O MODERATE
Withdrawals due to adverse events – betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											
2 Franz 1999 Jemec 2008	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/630 (0.95%)	7/170 (4.1%)	RR 0.19 (0.06 to 0.55)	33 fewer per 1000 (from 19 fewer to 39 fewer)	⊕⊕⊕O MODERATE
Withdrawals due to lack of efficacy - Betamethasone dipropionate OD (follow-up 8 weeks)											
1 Jemec 2008	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/518 (1.7%)	16/122 (13.1%)	RR 0.13 (0.06 to 0.29)	114 fewer per 1000 (from 93 fewer to 123 fewer)	⊕⊕⊕O MODERATE

(a) 2/2 unclear allocation concealment; 1/2 (75.6% weighted) higher drop-out rate in placebo group (8.5% of active group and 22.1% of placebo); 1/2 (24.4% weighted) unclear blinding and dropout rates not given by group

(b) 2/2 unclear allocation concealment and 1/2 (100% weighted) higher drop-out rate in placebo group (8.5% of active group and 22.1% of placebo)

(c) Unclear allocation concealment and higher drop-out rate in placebo group (8.5% of active group and 22.1% of placebo)

8.7.3.2 Evidence statements

In people with scalp psoriasis, topical potent corticosteroid treatment was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 4-8 weeks for betamethasone dipropionate once daily or betamethasone valerate twice daily [2 studies; 864 participants; moderate quality evidence][227,229]
- Patient's assessment at 4-8 weeks for betamethasone dipropionate once daily or betamethasone valerate twice daily (clear/nearly clear) [2 studies; 864 participants; moderate quality evidence] [227,229]
- Withdrawal due to adverse events at 4-8 weeks for betamethasone dipropionate once daily or betamethasone valerate twice daily [2 studies; 755 participants; moderate quality evidence][227,229]
- Withdrawal due to lack of efficacy at 8 weeks for betamethasone dipropionate once daily [1 study; 640 participants; moderate quality evidence] [229]

8.7.3.3 Heterogeneity

No significant heterogeneity was detected between the studies despite differences in treatment duration (4[227] vs 8[229] weeks); intervention (betamethasone valerate[227] vs dipropionate[229]); treatment frequency (once daily[229] versus twice daily[227]) and treatment formulation (gel[227] vs foam or lotion[227]).

One study[227] found that foam was significantly more effective at achieving response (investigator's assessment of clear/nearly clear) than lotion.

8.7.4 Very potent corticosteroid vs. placebo

8.7.4.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid (very potent)	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – clobetasol propionate OD/BD (follow-up 2-4 weeks)											

4 Franz2000 Olsen 1991 Jarratt 2004 Sofen2011	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	290/449 (64.6%)	27/339 (8%)	RR 8.55 (5.88 to 12.43)	601 more per 1000 (from 389 more to 910 more)	⊕⊕⊕O MODERATE
Patient's assessment (clear/nearly clear) – clobetasol propionate BD (follow-up 2 weeks)											
1 Franz2000	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77/125 (61.6%)	4/63 (6.3%)	RR 9.7 (3.72 to 25.3)	552 more per 1000 (from 173 more to 1000 more)	⊕⊕⊕O MODERATE
Skin atrophy – clobetasol propionate OD/BD (follow-up 4 weeks)											
2 Sofen2011 Jarratt 2004	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/135 (0%)	1/87 (1.1%)	RR 0.33 (0.01 to 7.76)	8 fewer per 1000 (from 11 fewer to 78 more)	⊕OOO VERY LOW
Withdrawals due to adverse events – clobetasol propionate OD/BD (follow-up 2-4 weeks)											
4 Franz2000 Jarratt 2004 Sofen2011 Olsen 1991	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	very serious[d]	none	0/445 (0%)	2/338 (0.59%)	RR 0.34 (0.04 to 3.25)	4 fewer per 1000 (from 6 fewer to 13 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy – clobetasol propionate OD/BD (follow-up 2-4 weeks)											
3 Olsen 1991 Franz2000 Jarratt 2004	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/408 (0.49%)	17/299 (5.7%)	RR 0.12 (0.03 to 0.5)	50 fewer per 1000 (from 28 fewer to 55 fewer)	⊕⊕⊕O MODERATE

(a) 4/4 unclear allocation concealment and 3/4 unclear blinding; 1/4 (22.9% weighted) unclear baseline comparability
(b) Unclear allocation concealment, blinding and baseline comparability
(c) 2/2 unclear allocation concealment; 1/2 unclear blinding
(d) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(e) 4/4 unclear allocation concealment; 3/4 unclear blinding; 1/4 unclear baseline comparability
(f) 3/3 unclear allocation concealment and blinding; 1/3 unclear baseline comparability

8.7.482 Evidence statements

In people with scalp psoriasis, topical very potent corticosteroid treatment was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 2-4 weeks for clobetasol propionate once or twice daily [4 studies; 788 participants; moderate quality evidence][225,226,237 243]
- Patient's assessment (clear/nearly clear) at 2 weeks for clobetasol propionate twice daily [1 study; 188 participants; moderate quality evidence] [225]
- Withdrawal due to lack of efficacy at 2-4 weeks for clobetasol propionate once or twice daily [3 studies; 707 participants; moderate quality evidence][225,226,237]

In people with scalp psoriasis, there was no statistically significant difference between topical very potent corticosteroid treatment and placebo for:

- Skin atrophy at 4 weeks for clobetasol propionate once or twice daily [2 studies; 222 participants; very low quality evidence] [226,243]
- Withdrawal due to adverse events at 2-4 weeks for clobetasol propionate once or twice daily [4 studies; 783 participants; very low quality evidence] [226 225,237,243]

8.7.4.3 Heterogeneity

No significant heterogeneity was detected between the studies despite differences in treatment duration (2[225,226] vs 4[237] weeks); treatment frequency (once daily[237] versus twice daily[225,226]) and treatment formulation (solution[226] vs shampoo[237] vs foam or lotion[225]).

One study[225] found that foam was more effective at achieving response (investigator's assessment of clear/nearly clear) than solution (although no statistics were presented).

8.7.5 Combined product containing potent corticosteroid and vitamin D analogue (betamethasone dipropionate and calcipotriol) vs. placebo

8.7.5.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and corticosteroid combination	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) (follow-up 8 weeks)											
1 Tyring 2010	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/135 (80%)	17/42 (50%)	RR 1.77 (1.21 to 2.58)	312 more per 1000 (from 85 more to 640 more)	⊕⊕⊕O MODERATE

Patient's assessment (clear/nearly clear) (follow-up 8 weeks)											
1 Tyring 2010	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	84/135 (62.2%)	15/42 (35.7%)	RR 1.74 (1.14 to 2.67)	264 more per 1000 (from 50 more to 596 more)	⊕⊕OO LOW
Withdrawal due to adverse events (follow-up 8 weeks)											
1 Tyring 2010	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	2/118 (1.7%)	0/34 (0%)	RR 1.47 (0.07 to 29.92)	-	⊕OOO VERY LOW

(a) Unclear allocation concealment
(b) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(c) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.7.5.2 Evidence statements

In people with scalp psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [1 study; 177 participants; moderate quality evidence][232]
- Patient's assessment (clear/nearly clear) at 8 weeks [1 study; 177 participants; low quality evidence][232]

In people with scalp psoriasis, there was no statistically significant difference between a combined product containing calcipotriol monohydrate and betamethasone dipropionate and placebo for:

- Withdrawal due to adverse events at 8 weeks [1 study; 152 participants; very low quality evidence][232]

8.7.5.3 Subgroups and heterogeneity

One study[232] performed a post-hoc subgroup analysis for the outcome of investigator's assessment of clear/nearly clear to assess any difference between black/African-American and Hispanic/Latino subgroups of people with psoriasis. No significant difference was seen between the subgroups, although the results significantly favoured the combination over placebo in the Hispanic/Latino group (78 participants), but showed no significant difference in the Black/African-American group (99 participants).

8.7.16 Very potent corticosteroid vs. placebo for maintenance of remission

One study assessed the efficacy and safety of clobetasol propionate compared with placebo as a maintenance treatment for up to 6 months among those who had achieved clear, very mild or mild disease during a 4-week induction phase with once-daily clobetasol propionate. During the maintenance phase clobetasol propionate was used twice-weekly (3 days apart), but once daily dosing was permitted for up to 4 weeks if relapse occurred.

8.7.16.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clobetasol propionate	Placebo	Relative (95% CI)	Absolute	
Duration of remission (N still in remission) - 1 month (follow-up 1 month)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	48/67 (71.6%)	30/69 (43.5%)	RR 1.65 (1.21 to 2.24)	283 more per 1000 (from 91 more to 539 more)	⊕OOO VERY LOW
Duration of remission (N still in remission) - 2 months (follow-up 2 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	41/67 (61.2%)	20/69 (29%)	RR 2.11 (1.39 to 3.2)	322 more per 1000 (from 113 more to 638 more)	⊕OOO VERY LOW
Duration of remission (N still in remission) - 3 months (follow-up 3 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	39/67 (58.2%)	13/69 (18.8%)	RR 3.09 (1.82 to 5.25)	394 more per 1000 (from 154 more to 801 more)	⊕OOO VERY LOW
Duration of remission (N still in remission) - 4 months (follow-up 4 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	34/67 (50.7%)	11/69 (15.9%)	RR 3.18 (1.76 to 5.75)	348 more per 1000 (from 121 more to 757 more)	⊕OOO VERY LOW
Duration of remission (N still in remission) - 5 months (follow-up 5 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	30/67 (44.8%)	10/69 (14.5%)	RR 3.09 (1.64 to 5.81)	303 more per 1000 (from 93 more to 697 more)	⊕OOO VERY LOW

Duration of remission (N still in remission) - 6 months (follow-up 6 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	27/67 (40.3%)	8/69 (11.6%)	RR 3.48 (1.7 to 7.1)	288 more per 1000 (from 81 more to 707 more)	⊕OOO VERY LOW
Median time to relapse (follow-up 6 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	serious[b]	serious[c]	none	67	69	-	Placebo: 30.5 days Clobetasol propionate: 141 days	⊕OOO VERY LOW
Skin atrophy (follow-up 6 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/67 (1.5%)	0/69 (0%)	RR 3.09 (0.13 to 74.5)	-	⊕OOO VERY LOW
Withdrawals due to adverse events (follow-up 6 months)											
1 Poulin 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/60 (3.3%)	0/52 (0%)	RR 4.34 (0.21 to 88.48)	-	⊕OOO VERY LOW

(a) Unclear allocation concealment and blinding and higher drop-out rate in placebo group; patients in vehicle group received active treatment if relapse occurred during maintenance phase
(b) Incorrect/less stringent definition of remission (at least mild on PGA)
(c) No range given
(d) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
Relapse data for this study is based on ITT analysis (worst case population; those who discontinued before relapse were considered as having relapse at the next visit)

8.7.662 Evidence statements

In people with scalp psoriasis, topical clobetasol propionate twice weekly maintenance treatment was statistically significantly better than placebo for:

- Maintenance of remission at 1-6 months [1 study; 136 participants; very low quality evidence][231]

In people with scalp psoriasis, there was no statistically significant difference between clobetasol propionate twice weekly maintenance treatment and placebo for:

- Skin atrophy at 6 months [1 study; 136 participants; very low quality evidence][231]
- Withdrawal due to adverse events at 6 months [1 study; 112 participants; very low quality evidence][231]

Evidence statement for individual study where no statistical analysis could be performed:

In people with psoriasis, clobetasol propionate twice weekly maintenance treatment was better than placebo for:

- Median time-to-relapse among those who had achieved remission (maximum follow-up of 6 months) [1 study; 136 participants; very low quality evidence][231].

8.7.37 Vitamin D or vitamin D analogue vs. potent corticosteroid

8.7.7.41 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogues	Corticosteroid (potent)	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – calcipotriol OD/BD vs betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											
3 Jemec 2008 Vande Kerkhof 2009 Klaber 1994	randomised trials	serious[a]	very serious[b]	no serious indirectness	no serious imprecision	none	362/794 (45.6%)	874/1350 (64.7%)	RR 0.69 (0.58 to 0.82)	201 fewer per 1000 (from 117 fewer to 272 fewer)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) – calcipotriol OD/BD vs betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											
3 Jemec 2008 Vande Kerkhof 2009 Klaber 1994	randomised trials	serious[a]	serious[c]	no serious indirectness	no serious imprecision	none	368/794 (46.3%)	856/1350 (63.4%)	RR 0.71 (0.62 to 0.82)	184 fewer per 1000 (from 114 fewer to 241 fewer)	⊕⊕OO LOW
Relapse rate - Calcipotriol BD vs betamethasone valerate BD (follow-up 4 weeks)											
1 Klaber 1994	randomised trials	serious[d]	no serious inconsistency	serious[e]	serious[f]	none	75/99 (75.8%)	102/129 (79.1%)	RR 0.96 (0.83 to 1.1)	32 fewer per 1000 (from 134 fewer to 79 more)	⊕OOO VERY LOW
Withdrawals due to adverse events – calcipotriol OD/BD vs betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											
3 Jemec 2008 Vande Kerkhof 2009 Klaber 1994	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/722 (5.4%)	15/1246 (1.2%)	RR 4.67 (2.57 to 8.48)	44 more per 1000 (from 19 more to 90 more)	⊕⊕⊕O MODERATE
Withdrawals due to lack of efficacy – calcipotriol OD/BD vs betamethasone dipropionate OD or betamethasone valerate BD (follow-up 4-8 weeks)											

3 Jemec 2008 Vande Kerkhof 2009 Klaber 1994	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/714 (4.3%)	20/1251 (1.6%)	RR 2.99 (1.73 to 5.19)	32 more per 1000 (from 12 more to 67 more)	⊕⊕⊕O MODERATE

(a) 3/3 unclear allocation concealment; 2/3 unclear blinding; 1/3 higher dropout in vitamin D or vitamin D analogue group (21.0% in vitamin D or vitamin D analogue group and 8.5% in corticosteroid group)

(b) Heterogeneity was present (I^2 = 76%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect)

(c) Heterogeneity was present (I^2 = 65%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect)

(d) Unclear allocation concealment and blinding

(e) Surrogate outcome for duration of remission (defined as an increase in the total sign score to at least 50% of the score at the start of double-blind treatment)

(f) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)

8.7.792 Evidence statements

In people with scalp psoriasis, topical potent corticosteroid treatment (betamethasone dipropionate once daily or betamethasone valerate twice daily) was statistically significantly better than topical vitamin D or vitamin D analogue (calcipotriol once or twice daily) for:

- Investigator's assessment (clear/nearly clear) at 4-8 weeks [3 studies; 2144 participants; very low quality evidence][229,233,236]
- Patient's assessment (clear/nearly clear) at 4-8 weeks [3 studies; 2144 participants; low quality evidence][229,233,236]
- Withdrawals due to adverse events at 4-8 weeks [3 studies; 1968 participants; moderate quality evidence][229,233,236]
- Withdrawals due to lack of efficacy at 4-8 weeks [3 studies; 1965 participants; moderate quality evidence][229,233,236]

In people with scalp psoriasis, there was no statistically significant difference between topical vitamin D analogue (calcipotriol twice daily) and potent corticosteroid (betamethasone valerate twice daily) for:

- Relapse rate after a maximum follow-up of 4 weeks post-treatment [1 study; 228 participants; very low quality evidence][236]

8.7.793 Heterogeneity

For the outcomes of investigator's and patient's assessment of achieving clear/nearly clear status high heterogeneity was present between the results for the three studies[229,233,236]. The heterogeneity was caused by the Jemec study in both cases, which gave a more favourable effect estimate for the potent corticosteroid. However, none of the pre-specified subgroups for investigation could explain this heterogeneity as there were no differences in study design or participant profile between the Jemec[229] and van de Kerkhof[233] studies. Although the Klaber study had a shorter treatment duration (4 vs 8 weeks), used twice rather than once daily dosing and betamethasone valerate solution rather than dipropionate gel, the result of this study was not the cause of the heterogeneity. However, the Jemec[229] study did have a high drop-out in the calcipotriol arm, which may have biased the results. Nevertheless, both studies

using betamethasone dipropionate suggest that there is precise evidence that potent corticosteroids are clinically beneficial in terms of achieving clearance or near clearance compared with vitamin D or vitamin D analogue treatment.

8.7.8 Vitamin D or vitamin D analogue vs. very potent corticosteroid

8.7.8.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogues	Corticosteroid (very potent)	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Calcipotriol (BD) vs clobetasol propionate (OD) (follow-up 4 weeks)											
1 Reygagne 2005	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	none	21/75 (28%)	38/76 (50%)	RR 0.56 (0.37 to 0.86)	220 fewer per 1000 (from 70 fewer to 315 fewer)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) - Calcipotriol (BD) vs clobetasol propionate (OD) (follow-up 4 weeks)											
1 Reygagne 2005	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	none	23/75 (30.7%)	36/76 (47.4%)	RR 0.65 (0.43 to 0.98)	166 fewer per 1000 (from 9 fewer to 270 fewer)	⊕OOO VERY LOW
Skin atrophy - Calcipotriol (BD) vs clobetasol propionate (OD) (follow-up 4 weeks)											
1 Reygagne 2005	randomised trials	serious[d]	no serious inconsistency	serious[b]	very serious[e]	Note that more cases of skin atrophy were present at baseline than week 4 and that in the clobetasol group it may only be 4 pts affected at different sites	1/64 (1.6%)	6/74 (8.1%)	RR 0.19 (0.02 to 1.56)	66 fewer per 1000 (from 79 fewer to 45 more)	⊕OOO VERY LOW
Withdrawals due to adverse events - Calcipotriol (BD) vs clobetasol propionate (OD) (follow-up 4 weeks)											
1 Reygagne 2005	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[f]	none	7/71 (9.9%)	0/73 (0%)	RR 15.42 (0.9 to 265)	-	⊕OOO VERY LOW

(a) Unclear allocation concealment; single blind (investigator); protocol violations included in ITT analysis; and relatively short duration of follow-up may produce an artificially high effect size in favour of the faster-acting clobetasol propionate
(b) Different administration schedules for 2 groups: clobetasol once daily and washed out; calcipotriol twice daily and not washout out
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit/harm to no clinically important benefit/harm)

(d) Unclear allocation concealment; single blind (investigator); protocol violations included in ITT analysis
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(f) Confidence interval ranges from clinically important effect to no effect

8.7.8.2 Evidence statements

In people with scalp psoriasis, topical very potent corticosteroid treatment (clobetasol propionate once daily) was statistically significantly better than topical vitamin D analogue (calcipotriol twice daily) for:

- Investigator's assessment (clear/nearly clear) at 4 weeks [1 study; 151 participants; very low quality evidence][230]
- Patient's assessment (clear/nearly clear) at 4 weeks [1 study; 151 participants; very low quality evidence][230]

In people with scalp psoriasis, there was no statistically significant difference between topical vitamin D analogue (calcipotriol twice daily) and very potent corticosteroid (clobetasol propionate once daily) for:

- Skin atrophy at 4 weeks [1 study; 138 participants; very low quality evidence][230]
- Withdrawals due to adverse events at 4 weeks [1 study; 144 participants; very low quality evidence][230]

8.7.9 Combined product containing vitamin D analogue and potent corticosteroid (betamethasone dipropionate and calcipotriol) vs. potent corticosteroid

8.7.9.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and corticosteroid combination	Potent corticosteroid	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) - Combination OD vs. betamethasone dipropionate OD (follow-up 8 weeks)											
2 Jemec 2008 van de Kerkhof 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	773/1180 (65.5%)	699/1118 (62.5%)	RR 1.12 (1.05 to 1.18)	75 more per 1000 (from 31 more to 113 more)	⊕⊕OO LOW

Patient's assessment (clear/nearly clear) - Combination OD vs. betamethasone dipropionate OD (follow-up 8 weeks)											
3 Buckley 2008 Jemec 2008 van de Kerkhof 2009	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	serious[b]	none	866/1216 (71.2%)	776/1228 (63.2%)	RR 1.13 (1.07 to 1.19)	82 more per 1000 (from 44 more to 120 more)	⊕⊕OO LOW
Withdrawals due to adverse events - Combination OD vs. betamethasone dipropionate OD (follow-up 8 weeks)											
3 Buckley 2008 Jemec 2008 van de Kerkhof 2009	randomised trials	serious[c]	serious[d]	no serious indirectness	very serious[e]	none	13/1107 (1.2%)	15/1122 (1.3%)	RR 0.88 (0.42 to 1.85)	2 fewer per 1000 (from 8 fewer to 11 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy - Combination OD vs. betamethasone dipropionate OD (follow-up 8 weeks)											
3 Buckley 2008 Jemec 2008 van de Kerkhof 2009	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	serious[f]	none	9/1103 (0.82%)	20/1127 (1.8%)	RR 0.47 (0.22 to 1.01)	9 fewer per 1000 (from 14 fewer to 0 more)	⊕⊕OO LOW

(a) 2/2 unclear allocation concealment; 1/2 unclear blinding
(b) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(c) 3/3 unclear allocation concealment; 2/3 unclear blinding
(d) No heterogeneity detected statistically due to very wide confidence intervals but studies show different directions of effect
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(f) Confidence interval ranges from clinically important effect to no effect

8.7.972 Evidence statements

In people with scalp psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate was statistically significantly better than potent corticosteroid alone (betamethasone dipropionate once daily) for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [2 studies; 1472 participants; low quality evidence][228,229,233]
- Patient's assessment (clear/nearly clear) [3 studies; 2226 participants; low quality evidence] [228,229,233]

In people with scalp psoriasis, there was no statistically significant difference between a combined product containing calcipotriol monohydrate and betamethasone dipropionate and potent corticosteroid alone (betamethasone dipropionate once daily) for:

- Withdrawal due to adverse events at 8 weeks [3 studies; 2229 participants; very low quality evidence][228,229,233]
- Withdrawal due to lack of efficacy at 8 weeks [3 studies; 2230 participants; low quality evidence][228,229,233]

8.7.9 Heterogeneity

No significant heterogeneity was detected between the studies and all had the same treatment duration, formulation and frequency as well as the same inclusion criteria in terms of disease severity.

8.7.10 Combined product containing vitamin D analogue and potent corticosteroid (betamethasone dipropionate and calcipotriol) vs. vitamin D or vitamin D analogue

One study[241] assessed long-term (52 weeks) treatment for this comparison. This study used a once daily administration schedule as required by the participants and the mean treatment duration was 44 weeks and 37 weeks for the combination and vitamin D or vitamin D groups, respectively (mean weekly weight used: 10.6g in two compound group and 12.8g in calcipotriol group; mean weight used over whole study period 470.8g and 440.0g, respectively).

8.7.10.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D and corticosteroid combination	Vitamin D or vitamin D analogue	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – combination OD vs calcipotriol OD/BD (follow-up 8 weeks)											

3 Kragballe2009 Jemec 2008 van de Kerkhof 2009	randomised trials	very serious[a]	serious[b]	no serious indirectness	no serious imprecision	none	915/1315 (69.6%)	257/663 (38.8%)	RR 1.83 (1.52 to 2.20)	322 more per 1000 (from 202 more to 465 more)	⊕OOO VERY LOW
Patient's assessment (clear/nearly clear) - combination OD gel vs calcipotriol OD gel (follow-up 8 weeks)											
2 Jemec 2008 van de Kerkhof 2009	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	766/1108 (69.1%)	232/558 (41.6%)	RR 1.66 (1.5 to 1.85)	274 more per 1000 (from 208 more to 353 more)	⊕⊕OO LOW
Patient's assessment (clear/nearly clear) - combination OD gel vs calcipotriol BD solution (follow-up 8 weeks)											
1 Kragballe2009	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	170/207 (82.1%)	36/105 (34.3%)	RR 2.4 (1.82 to 3.15)	480 more per 1000 (from 281 more to 737 more)	⊕⊕OO LOW
Skin atrophy - combination OD vs calcipotriol BD (follow-up 8 weeks)											
1 Kragballe2009	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/207 (0%)	0/105 (0%)	not pooled	not pooled	⊕⊕OO LOW
Skin atrophy - combination OD vs calcipotriol OD (follow-up 52 weeks)											
1 Luger 2008	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/429 (0%)	0/440 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Relapse rate - combination OD vs calcipotriol BD (follow-up 8 weeks)											
1 Kragballe2009	randomised trials	very serious[f]	no serious inconsistency	serious[g]	serious[h]	none	73/135 (54.1%)	10/29 (34.5%)	RR 1.57 (0.93 to 2.65)	197 more per 1000 (from 24 fewer to 569 more)	⊕OOO VERY LOW
Median time to relapse - combination OD vs calcipotriol BD											
1 Kragballe2009	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	serious[i]	none	135	29	Combination: 35 days Vitamin D analogue: 58 days		⊕OOO VERY LOW
Withdrawals due to adverse events - combination OD vs calcipotriol OD/BD (follow-up 8 weeks)											
3 Kragballe2009 Jemec 2008	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/1204 (1.2%)	37/582 (6.4%)	RR 0.18 (0.1 to 0.33)	52 fewer per 1000 (from 43 fewer to 57 fewer)	⊕⊕OO LOW

van de Kerkhof 2009											
Withdrawals due to lack of efficacy - combination OD vs calcipotriol OD (follow-up 8 weeks)											
2 Jemec 2008 van de Kerkhof 2009	randomised trials	very serious[j]	very serious[k]	no serious indirectness	very serious[j]	none	9/1009 (0.89%)	27/490 (5.5%)	RR 0.16 (0.02 to 1.35)	46 fewer per 1000 (from 54 fewer to 19 more)	⊕OOO VERY LOW
Withdrawals due to adverse events - combination OD vs calcipotriol OD (follow-up 52 weeks)											
1 Luger 2008	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/346 (2.6%)	44/309 (14.2%)	RR 0.18 (0.09 to 0.37)	117 fewer per 1000 (from 90 fewer to 130 fewer)	⊕⊕⊕O MODERATE
Withdrawals due to lack of efficacy - combination OD vs calcipotriol OD (follow-up 52 weeks)											
1 Luger 2008	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/351 (4%)	51/316 (16.1%)	RR 0.25 (0.14 to 0.44)	121 fewer per 1000 (from 90 fewer to 139 fewer)	⊕⊕⊕O MODERATE

(a) 3/3 unclear allocation concealment; 1/3 (48.2% weighted) unclear blinding; 1/3 single blind (investigator); 2/3 higher dropout with vitamin D or vitamin D analogue
(b) Heterogeneity was present (I^2 = 64%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect and the p-value for chi squared was >0.05)
(c) 2/2 unclear allocation concealment; 1/2 single blind (investigator); 1/2 higher dropout rate in vitamin D or vitamin D analogue group (22.1% vs 11.3% in combination group)
(d) Unclear allocation concealment; single blind (investigator); higher dropout in vitamin D or vitamin D analogue group (21.9% vs 8.2% in combination group)
(e) Unclear allocation concealment
(f) Unclear allocation concealment; single blind (investigator); higher dropout in vitamin D or vitamin D analogue group (21.9% vs 8.2% in combination group); also, unclear baseline comparability as only includes those in each group who achieved remission; therefore, there are also fewer participants in the vitamin D or vitamin D analogue group
(g) Surrogate outcome for duration of remission
(h) Confidence interval ranges from clinically important effect to no effect
(i) No range given
(j) 2/2 unclear allocation concealment; 1/2 unclear blinding; 1/2 higher dropout rate in vitamin D or vitamin D analogue group (22.1% vs 11.3% in combination group)
(k) Heterogeneity was present (I^2 = 80%) that could not be explained by pre-defined subgroups (however, all studies showed the same direction of effect)
(l) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.7.10.2 Evidence statements

In people with scalp psoriasis, a combined product containing calcipotriol monohydrate and betamethasone dipropionate was statistically significantly better than vitamin D analogue alone (calcipotriol once or twice daily) for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [3 studies; 1978 participants; very low quality evidence][229,233,234]
- Patient's assessment (clear/nearly clear) at 8 weeks [3 studies; 1978 participants; low quality evidence][229,233,234]
- Withdrawals due to adverse events at 8 weeks [3 studies; 1786 participants; low quality evidence][229,233,234]

- Withdrawals due to adverse events at 52 weeks [1 study; 655 participants; moderate quality evidence][241]
- Withdrawals due to lack of efficacy at 52 weeks [1 study; 667 participants; moderate quality evidence][241]

In people with scalp psoriasis, there were no events with either a combined product containing calcipotriol monohydrate and betamethasone dipropionate or vitamin D analogue alone (calcipotriol once or twice daily) for:

- Skin atrophy at 8 or 52 weeks [2 studies; 312 and 869 participants; low to moderate quality evidence][234,241]

In people with scalp psoriasis, there was no statistically significant difference between a combined product containing calcipotriol monohydrate and betamethasone dipropionate and topical vitamin D analogue alone for:

- Relapse rate at 8 weeks post-treatment for the combined product compared with calcipotriol twice daily [1 study; 164 participants; very low quality evidence][234]
- Withdrawals due to lack of efficacy at 8 weeks for the combined product compared with calcipotriol once daily [2 studies; 1499 participants; very low quality evidence][229,233]

Evidence statement for an individual study where no statistical analysis could be performed comparing a combined product containing calcipotriol monohydrate and betamethasone dipropionate and vitamin D analogue alone for scalp psoriasis:

- The median time to relapse was longer with calcipotriol twice daily than with the combination treatment after a maximum follow-up of 8 weeks post-treatment [1 study; 164 participants; very low quality evidence][234]

8.7.1063 Heterogeneity

For the outcome of investigator's assessment of achieving clear/nearly clear status high heterogeneity was present between the results for the three studies[229,233,234]. The heterogeneity was caused by the van de Kerkhof study, which gave an effect estimate that was slightly less favourable for the combination. However, none of the pre-specified subgroups for investigation could explain this heterogeneity as there were no differences in study design or participant profile between the Jemec[229] and van de Kerkhof[233] studies. Although the Kragballe study[234] used twice rather than once daily dosing of calcipotriol, the result of this study was not the cause of the heterogeneity. Differences in risk of bias did not explain the inconsistency either. Nevertheless, all three studies demonstrate that there is precise evidence that the combination is clinically beneficial in terms of achieving clearance or near clearance compared with vitamin D or vitamin D analogue treatment alone.

For the patient's assessment of achieving clear/nearly clear status high heterogeneity was present between the results for the three studies[229,233,234]. This was explained by creating subgroups based on the treatment formulation, as the Kragballe 2009[234] study used a gel for the combination arm and a solution for the calcipotriol arm, which resulted in a greater effect estimate in favour of the combination treatment. Note that although the treatment frequency was also different in the Kragballe 2009[234] study (twice daily calcipotriol compared with once daily in the other two studies[229,233,234]) this is not a clinically relevant explanation for the heterogeneity as the study with twice daily calcipotriol[234] favours the combination more highly.

8.7.11 Very potent corticosteroid vs. coal tar polytherapy

8.7.11.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Very potent corticosteroid	Coal tar polytherapy	Relative (95% CI)	Absolute	
Skin atrophy - Clobetasol propionate OD vs polytar twice weekly (follow-up 4 weeks)											
1 Griffiths2006A	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/121 (0%)	0/41 (0%)	not pooled	not pooled	⊕⊕OO LOW
Withdrawal due to adverse events - Clobetasol propionate OD vs polytar twice weekly (follow-up 4 weeks)											
1 Griffiths2006A	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/121 (0.83%)	0/41 (0%)	RR 1.03 (0.04 to 24.87)	-	⊕OOO VERY LOW

(a) Unclear allocation concealment and blinding; unclear dropout rates; higher proportion of males in the tar group (65.9% vs 48.8%)
(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.7.11.2 Evidence statements

In people with scalp psoriasis, there were no events with either very potent corticosteroid (clobetasol propionate once daily) or coal tar polytherapy twice weekly for:

- Skin atrophy at 4 weeks [1 study; 162 participants; low quality evidence][239]

In people with scalp psoriasis, there was no statistically significant difference between very potent corticosteroid (clobetasol propionate once daily)and coal tar polytherapy twice weekly for:

- Withdrawal due to adverse events at 4 weeks [1 study; 162 participants; very low quality evidence][239]

8.7.112 Vitamin D analogue vs. coal tar polytherapy

8.7.1221 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcipotriol	Coal tar polytherapy	Relative (95% CI)	Absolute	
Investigators assessment (at least moderate improvement) - Calcipotriol BD vs. coal tar polytherapy OD (follow-up 8 weeks)											
1 McKinnon2000	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	120/210 (57.1%)	79/213 (37.1%)	RR 1.54 (1.25 to 1.9)	200 more per 1000 (from 93 more to 334 more)	⊕OOO VERY LOW
Withdrawals due to adverse events - Calcipotriol BD vs. coal tar polytherapy OD (follow-up 8 weeks)											
1 McKinnon2000	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/230 (15.2%)	16/215 (7.4%)	RR 2.04 (1.17 to 3.59)	77 more per 1000 (from 13 more to 193 more)	⊕⊕OO LOW

(a) Unclear allocation concealment; unblinded; high dropout rate (30.3% in vitamin D analogue and 29.1% in tar group)
(b) Incorrect definition of response (at least moderate improvement)

8.7.1262 Evidence statements

In people with scalp psoriasis, vitamin D analogue (calcipotriol twice daily) was statistically significantly better than coal tar polytherapy (once daily) for:

- Investigator's assessment (at least moderate improvement) at 8 weeks [1 study; 423 participants; very low quality evidence][235]

In people with scalp psoriasis, coal tar polytherapy (once daily) was statistically significantly better than vitamin D analogue (calcipotriol twice daily) for:

- Withdrawal due to adverse events at 8 weeks [1 study; 445 participants; low quality evidence][239]

8.8 Scalp psoriasis – time to remission

8.8.1 Vitamin D or vitamin D analogues

8.8.1.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcipotriol		
Time-to-absent/very mild disease (follow-up 1 week)									
1 Jemec2011 (pooled data from Jemec2008 & van de Kerkhof 2009)	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	558	Patients achieving absent or very mild disease Week 1: 54/545 (10.0%)	⊕⊕OO LOW
Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 Jemec 2008	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	272	Patients achieving absent or very mild disease Week 2: 51 (18.8%) Week 4: 64 (23.5%) Week 8: 100 (36.8%)	⊕⊕OO LOW
Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 van de Kerhof2009	observational studies[a]	no serious risk of	no serious inconsistency	no serious indirectness	no serious imprecision	none	286	Patients achieving absent or very mild disease Week 2: 45 (15.7%)	⊕⊕OO LOW

		bias[b]						Week 4: 74 (25.9%) Week 8: 124 (43.4%)	
Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 Kragballe 2009	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	Patients achieving absent or very mild disease Week 2: 11 (10.5%) Week 4: 19 (18.1%) Week 8: 33 (31.4%)	⊕⊕OO LOW
Mean time to maximum response (change in TSS) (follow-up 24 weeks)									
1 McKinnon 2000	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	very serious[e]	none	238	Based on change in TSS maximum effect was not reached by the end of 8 weeks comparative phase Over the long-term treatment phase based on graphical representation of change in TSS most of the improvement is achieved by 12 weeks, with only slight further improvement up to 24 weeks (approximately 1 point reduction on TSS over 12 weeks)	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm
(b) Unclear allocation concealment may have biased patient selection for this intervention
(c) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (21.0%)
(d) Incorrect outcome measure
(e) Interpreted from graphical representation

8.8.172 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical vitamin D or vitamin D analogues (no statistical analysis could be performed).

In people with scalp psoriasis, the time to remission when using calcipotriol varied between studies:

- Proportion achieving remission by 8 weeks ranged from 31.4 to 43.4% [3 studies; 663 participants; low quality evidence][229,233,234]

- The continued increase in responders between 4 and 8 weeks ranged from 13.3-17.5% [3 studies; 663 participants; low quality evidence][229,233,234]
- Some people (10%) achieved remission by 1 week [1 study; 558 participants; low quality evidence][242]
- Of those who achieved remission by the end of the trial (8 weeks), 57.6-64.0% had responded by week 4 based on investigators assessment [3 studies; 663 participants; low quality evidence][229,233,234]
- Graphical representation of longer-term data demonstrated that the majority of the improvement in TSS score is achieved by 12 weeks, with only slight further improvement up to 24 weeks (approximately 1 point reduction on TSS over the second 12 weeks) [1 study; 238 participants; very low quality evidence][235]

8.8.183 Summary

The evidence suggests that maximum response is not achieved in all patients by 8 weeks, with the response rate still increasing at this time point [229,233,234], and one study[235] suggests that 12 weeks may represent the time at which maximum response is achieved.

8.822 Potent corticosteroids

8.8.231 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betamethasone dipropionate		
Time-to-absent/very mild disease (follow-up 1 week)									
1 Jemec2011 (pooled data from Jemec2008 & van de Kerkhof 2009)	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1118	Patients achieving absent or very mild disease Week 1: 262 (24.1%)	⊕⊕OO LOW

Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 Jemec 2008	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	562	Patients achieving absent or very mild disease Week 2: 262 (47.1%) Week 4: 304 (54.7%) Week 8: 356 (64.0%)	⊕⊕OO LOW
Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 van de Kerhof2009	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	556	Patients achieving absent or very mild disease Week 2: 216 (38.4%) Week 4: 287 (51.1%) Week 8: 343 (61.0%)	⊕⊕OO LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm

(b) Unclear allocation concealment may have biased patient selection for this intervention

(c) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (21.0%)

8.8.2.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical potent corticosteroids (no statistical analysis could be performed).

In people with scalp psoriasis, the time to remission when using betamethasone dipropionate varied between studies:

- Proportion achieving remission by 8 weeks ranged from 61.0 to 64.0% [2 studies; 1118 participants; low quality evidence][229,233]
- The continued increase in responders between 4 and 8 weeks ranged from 9.3-9.9% [2 studies; 1118 participants; low quality evidence][229,233]
- Some people (24.1%) achieved remission by 1 week [1 study; 262 participants; low quality evidence][242]
- Of those who achieved remission by the end of the trial (8 weeks), 63.0-73.6% had responded by week 2 and 83.7-85.4% by week 4 based on investigators assessment [2 studies; 1118 participants; low quality evidence][229,233]

8.8.213 Summary

The evidence suggests that maximum response is not achieved in all patients by 8 weeks, with the response rate still increasing at this time point [229,233].
However, the majority of those who will respond within 8 weeks had done so by week 4.

8.843 Very potent corticosteroids

8.8.351 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clobetasol propionate		
Time-to-clear/nearly clear disease (follow-up 4 weeks)									
1 Sofen 2011	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81	Patients achieving clear/nearly clear disease Week 2: 33/41 (80.5%) Week 4: 35/41 (85.4%)	⊕⊕OO LOW
Mean time to maximum response (TSS) (follow-up 4 weeks)									
1 Reygagne 2005	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[c]	very serious[d]	none	232	Graphical representation of mean TSS over time shows a large effect by week 2 which begins to slow between weeks 2-4, with continued gradual reduction in mean TSS)	⊕OOO VERY LOW
Mean time to maximum response (TSS) (follow-up 4 weeks)									
1 Jarratt 2004	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[c]	very serious[d]	none	95	Score for TSS decreased rapidly from baseline to week four, but did not reach maximum effect (2-wk post-treatment follow-up showed a slight increase in TSS)	⊕OOO VERY LOW
Mean time to maximum response (TSS) (follow-up 2 weeks)									
1 Franz 2000	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[c]	very serious[d]	none	125	Maximum effect was not reached for scaling, plaque thickness, pruritus and erythema scores by 14 days; the mean severity score	⊕OOO VERY LOW

								increased during the 14 days following removal of treatment	
Mean time to maximum response (PAGI) (follow-up 4 weeks)									
1 Griffiths 2006A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[d]	none	121	Continued improvement was seen between weeks 2 and 4 based on improvement in participants' global assessment of improvement from baseline	⊕OOO VERY LOW
Mean time to remission (PGA) (follow-up 4 weeks)									
1 Poulin 2010	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[e]	no serious imprecision	none	67	89% (141/168) of those entered into the induction phase achieved clear, mild or very mild disease after 4 weeks of treatment	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm
(b) Unclear allocation concealment may have biased patient selection for this intervention
(c) Incorrect outcome measure
(d) Interpreted from graphical representation
(e) Incorrect definition of response (at least mild on PGA)

8.8.3.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical very potent corticosteroids (no statistical analysis could be performed).

- In people with scalp psoriasis, the time to remission when using clobetasol propionate varied between studies:
- Proportion achieving remission by 4 weeks was 85.4% [1 study; 81 participants; low quality evidence][243]
- The continued increase in responders between 2 and 4 weeks was 4.9% [1 study; 81 participants; low quality evidence][243]
- Of those who achieved remission by the end of the trial (4 weeks), 94.3% had responded by week 2 [1 study; 81 participants; low quality evidence][243]
- Mean TSS shows a rapid effect over the first 2 weeks of treatment, but has not reached a maximum effect by week 2 or 4 [3 studies; 452 participants; very low quality evidence][225,230,237]
- Patient's global improvement scores show that continued improvement was seen between weeks 2 and 4 [1 study; 121 participants; very low quality evidence][239]
- Investigator's global assessment of response (clear, mild or very mild disease) showed that 89% achieved remission by week 4 [1 study; 67 participants; very low quality evidence][231].

8.8.313 Summary

The evidence suggests that maximum response is not achieved in all patients by 2 or 4 weeks, with the response rate still increasing at this time point[225,230,231,237,239].

8.844 Combined product containing potent corticosteroid and vitamin D analogue (betamethasone dipropionate and calcipotriol monohydrate)

8.8.451 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined betamethasone dipropionate and calcipotriol		
Time-to-absent/very mild disease (follow-up 1 week)									
1 Jemec2011 (pooled data from Jemec2008 & van de Kerkhof 2009)	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1108	Patients achieving absent or very mild disease Week 1: 331 (30.6%)	⊕⊕OO LOW
Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 Jemec 2008	observational studies[a]	no serious risk of bias[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	541	Patients achieving absent or very mild disease Week 2: 311 (57.5%) Week 4: 362 (66.9%) Week 8: 385 (71.2%)	⊕⊕OO LOW

Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 van de Kerhof2009	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	567	Patients achieving absent or very mild disease Week 2: 278 (49.0%) Week 4: 311 (54.9%) Week 8: 388 (68.4%)	⊕⊕OO LOW
Time-to-absent/very mild disease (follow-up 2-8 weeks)									
1 Kragballe 2009	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	207	Patients achieving absent or very mild disease Week 2: 125 (60.4%) Week 4: 114 (55.1%) Week 8: 142 (68.6%)	⊕⊕OO LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm

(b) Unclear allocation concealment may have biased patient selection for this intervention

(c) Unclear allocation concealment may have biased patient selection for this intervention and there was a high rate of dropout (21.0%)

8.8.4.62 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical combination therapies (no statistical analysis could be performed).

In people with scalp psoriasis, the time to remission when using a combined product containing betamethasone dipropionate and calcipotriol varied between studies:

- Proportion achieving remission by 8 weeks ranged from 68.4 to 71.2% [3 studies; 1315 participants; low quality evidence][229,233,234]
- The continued increase in responders between 4 and 8 weeks ranged from 4.3-13.5% [3 studies; 1315 participants; low quality evidence][229,233,234]
- Some people (30.6%) achieved remission by 1 week [1 study; 1108 participants; low quality evidence][242]
- Of those who achieved remission by the end of the trial (8 weeks), 71.6-88.0% had responded by week 2 and 80.2-94.0% by week 4 based on investigators assessment [3 studies; 1315 participants; low quality evidence][229,233,234]

8.8.4 Summary

- The evidence suggests that maximum response is not achieved in all patients by 8 weeks, with the response rate still increasing at this time point[229,233,234]. However, the majority of those who will respond within 8 weeks had done so by weeks 2-4.

8.8.5 Coal tar

8.8.5.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Coal tar		
Mean time to maximum response (change in TSS) (follow-up 8 weeks)									
1 McKinnon 2000	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[c]	very serious[d]	none	237	Based on change in TSS maximum effect was not reached by the end of the study period (8 weeks)	⊕OOO VERY LOW
Mean time to maximum response (patients' assessment) (follow-up 4 weeks)									
1 Griffiths 2006A	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[d]	none	41	A very small amount of continued improvement was seen between weeks 2 and 4 based on change in participants' global assessment of improvement from baseline	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm

(b) Unclear allocation concealment may have biased patient selection for this intervention

(c) Incorrect outcome measure

(d) Interpreted from graphical representation

8.8.5.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical coal tar therapies (no statistical analysis could be performed).

In people with scalp psoriasis, the time to remission when using coal tar varied between studies:

- Mean change in TSS showed that a maximum effect was not reached by week 8 [1 study; 237 participants; very low quality evidence][235]
- Patient's assessment of global improvement showed that very slight continued improvement was seen between weeks 2 and 4 [1 study; 41 participants; very low quality evidence][239]

8.8.553 Summary

The evidence suggests that maximum response based on TSS is not achieved in all patients by 8 weeks, with the response rate still increasing at this time point[235], although the results at 4 weeks suggest that response based on patient's global assessment may begin to plateau between 2 and 4 weeks[239].

8.8.16 Network meta-analysis – scalp psoriasis

Based on the results of conventional meta-analyses of direct evidence alone, it can be difficult to determine which intervention is most effective in the treatment of chronic plaque psoriasis. The challenge of interpretation arises for two reasons:

- Some pairs of alternative strategies have not been directly compared in a randomised controlled trial (for example, very potent corticosteroid vs a combined product containing vitamin D analogue and potent corticosteroid)
- There are frequently multiple overlapping comparisons (for example vitamin D or vitamin D analogue vs potent corticosteroid, vitamin D or vitamin D analogue vs a combined product containing vitamin D analogue and potent corticosteroid and potent corticosteroid vs a combined product containing vitamin D analogue and potent corticosteroid) that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy, defined as the achievement of clearance or near clearance. A network meta-analysis also provides estimates of effect (with 95% credible interval) for each intervention compared to one another and compared to a single baseline risk. These estimates provide a useful and coherent clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness of the topical therapies in the original cost-effectiveness modelling outlined in section 8.9. For details on the methods, results and interpretation of the network meta-analyses, see Appendix L.

The inclusion criteria for and intervention compared in the NMA were the same as in the review of direct evidence (Section 8.6.1). A class effect was still assumed, but in order to reduce heterogeneity in the network of evidence, interventions were broken down by treatment frequency from the outset. In other words, once daily vitamin D or vitamin D analogue and twice daily vitamin D or vitamin D analogue were considered separate comparators in the NMA. Placebo/vehicle delivered once daily was also considered separately from twice daily placebo/vehicle.

The outcomes considered as part of the NMA were restricted to those measuring response:

- Clear/nearly clear or marked improvement (at least 75% improvement) on Investigator's assessment of overall global improvement (IAGI) or clear/nearly clear/minimal (not mild) on Physician's Global Assessment (PGA)

Unfortunately, the network of evidence for the outcome of clear/nearly clear or marked improvement (at least 75% improvement) on the Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment was not connected such that an analysis could be performed.

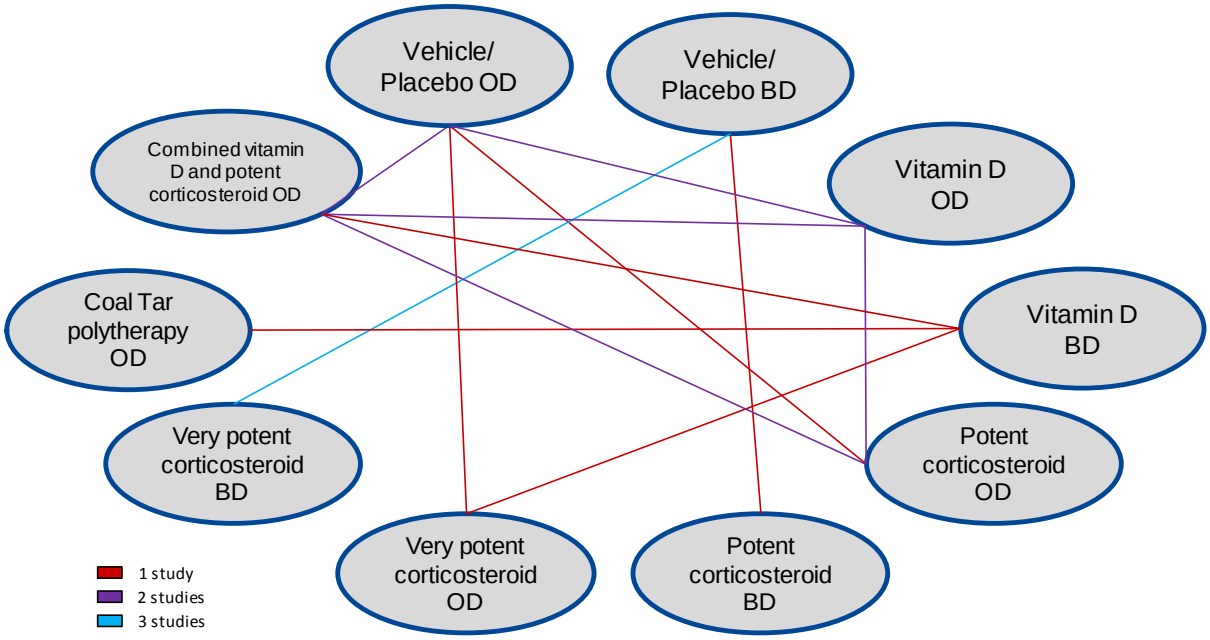
8.8.17 Results of NMA for investigator assessed outcome: clear/nearly clear (IAGI/PGA)

A total of 13 studies[225-227,229,230,232-237,240,243] from the original evidence review met the inclusion criteria for the network.

Figure 1 presents all the interventions included in the NMA as well as shows where there is direct evidence for a particular comparison and the number of studies that have included that comparison. For example, there are 3 studies reporting the outcome 'clear' or 'nearly clear' as measured by IAGI or PGA for the comparison of twice daily vehicle/placebo and twice daily very potent corticosteroid. The diagram also highlights where there are gaps in the direct evidence. For example, there are no

studies comparing a combined product containing vitamin D or vitamin D analogue and potent corticosteroid to very potent corticosteroid.

Figure 6: Clear or nearly clear – IAGI and PGA



Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the analysis.

The results of the network meta-analysis in terms of the relative risk of each intervention compared to twice daily vehicle/placebo are presented in Table 71. It also gives a probability that the intervention is the most effective overall.

Table 71: Relative risks of clear/nearly clear on IAGI/PGA for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower CrI	Upper CrI	Probability most effective
Very potent corticosteroid BD	6.946	5.583	7.962	59.0%
Combined product containing calcipotriol monohydrate and betamethasone dipropionate OD	6.459	3.18	8.365	22.3%
Potent corticosteroid OD	6.135	2.752	8.433	12.2%
Very potent corticosteroid OD	5.228	1.991	8.006	5.9%
Potent corticosteroid BD	4.448	2.255	6.702	0.4%
Vitamin D or vitamin D analogue OD	4.002	1.175	7.686	0.1%
Vitamin D or vitamin D analogue BD	3.149	1.364	5.993	0.0%
Placebo OD	2.345	0.5069	6.36	0.0%
Coal Tar polytherapy OD	1.732	0.4415	5.263	0.1%

8.8.791 Evidence statements

Results of the network meta-analysis of randomised controlled trials indicate that in the treatment of patients with psoriasis the following interventions are statistically significantly more effective than

twice daily vehicle/placebo at inducing clearance/near clearance as measured by the investigator or physician (IAGI/PGA):

- Once and twice daily very potent corticosteroid
- Once and twice daily potent corticosteroid
- Once and twice daily vitamin D or vitamin D analogue
- Once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate

Results of the network meta-analysis of randomised controlled trials indicate that in the treatment of patients with scalp psoriasis there is no statistically significant difference between once daily coal tar polytherapy and twice daily placebo in terms of achieving clearance/near clearance as measured by the investigator or physician (IAGI/PGA).

Results of the network meta-analysis indicate that there are very few comparisons between active treatments for which the treatment effect reaches statistical significance. A few exceptions include:

- Once daily potent corticosteroid is more effective than once or twice daily vitamin D or vitamin D analogue
- Once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate is more effective than once or twice daily vitamin D or vitamin D analogue.
- Twice daily very potent corticosteroid is more effective than twice daily vitamin D or vitamin D analogue.
- Once daily potent corticosteroid, once and twice daily very potent corticosteroid and once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate are more effective than once daily coal tar polytherapy.

Results of the network meta-analysis indicate that there is no statistically significant difference between once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate and once or twice daily very potent corticosteroids. Results show a non-significant trend toward combined product containing calcipotriol monohydrate and betamethasone dipropionate being more effective than once daily very potent corticosteroid; however, the results also show a non-significant trend toward twice daily very potent corticosteroid being more effective than combined product containing calcipotriol monohydrate and betamethasone dipropionate.

8.9 Cost effectiveness evidence (scalp psoriasis)

8.9.1 Economic evidence – literature review (scalp psoriasis)

One study[244] was included that included relevant comparisons. It is summarised in the economic evidence profile below (Table 72 and Table 73). See also the full study evidence tables in Appendix I. No studies were excluded.

Table 72: Economic study characteristics

Study	Limitations	Applicability	Other comments
Affleck[244]	Potentially serious limitations (a)	Directly applicable (b)	CUA based on indirect published data. Scottish payer perspective; Population was exclusively scalp psoriasis patients.

(a) Sufficient time horizon of 1 year. The cost and effect sources informing clinical review need to be reviewed, one parameter used expert opinion. Appropriate health outcomes used (Response, non-response, relapse, AEs). Incremental results inappropriately presented, but appropriate incremental analysis possible from data presented. Deterministic sensitivity analysis, no probabilistic analysis.

(b) Used Scottish NHS perspective. Population and intervention appropriate for guideline. Quality of life assessment used SF-36 gathered during RCT mapped to SF-6D.

Table 73: Economic summary of findings

Study	Interventions compared	Incremental cost	Incremental effects (QALYS)	Incremental Cost effectiveness	Uncertainty
Affleck(a)					
	BDP OD → Calcipotriol BD → Capasal OD Vs. BMV BD→ Calcipotriol & BDP→ TFC gel OD	£5.96 (b)	0.0016	£3,725 per QALY	Despite extensive deterministic sensitivity analysis, the presentation of results does not allow analysis how parameter uncertainty would affect the incremental results when comparing individual strategies.

(a) Affleck et al. considered 12 possible treatment sequences. Other comparators in the study included 'Calcipotriol & Polytar' and Calcipotriol OD. Further details of the multiple comparisons can be found in the evidence table presented in Appendix I. Ten sequences were dominated by the sequence BMV BD → Calcipotriol + BDP → TCF OD.

(b) Costs incorporated: Topicals, costs of failure (GP visits, outpatient dermatology visits, day clinics, topicals on waiting list); excluded costs of additional treatments for treatment failures (e.g. phototherapy). These costs were estimated using: MIMS, PSSRU, Scottish reference costs.

Although not presented in the above profile because they were dominated, it is worth noting themes from the overall analysis of all 12 treatment comparators. Overall, strategies that did not include combined or concurrent vitamin D or vitamin D analogue and potent corticosteroids (one applied in the morning and one in the evening) generated fewer QALYs and higher costs than those that did. In fact, the analysis showed that a strategy of starting with vitamin D or vitamin D analogue once daily and escalating to twice daily and then moving finally to Capasal (salicylic acid and coal tar shampoo) once daily was the most costly and the least effective of all 12 strategies.

There was little difference between the overall effectiveness (QALYs gained) of strategies depending upon when in the sequence the combined product containing calcipotriol monohydrate and betamethasone dipropionate came (first-, second- or third-line). Costs also did not seem to follow a pattern based on where combination product came in the sequence, but seemed to be driven more by what other treatments were in the sequence (e.g. once or twice daily vitamin D or vitamin D analogue and/or potent corticosteroid).

8.9.2 Economic evidence – original economic analysis (scalp psoriasis)

The review of clinical evidence for topical therapies used in the treatment of individuals with moderate to severe scalp psoriasis showed that there were several treatment options – tars, corticosteroids (potent and very potent), vitamin D or vitamin D analogues and combination products – each associated with certain advantages and disadvantages. The results of the network meta-analysis indicated that some interventions, such as very potent corticosteroid as well as combined product containing calcipotriol monohydrate and betamethasone dipropionate, were more likely to induce clearance or near clearance than others. Given that these combined and concurrent application strategies carry additional cost compared to both their individual constituent parts and compared to other topical alternatives, it was important to consider whether these additional costs are justified by additional health benefits in terms of improved quality of life.

The choice of which topical therapy to offer patients with moderate to severe scalp psoriasis in primary care was identified as among the highest economic priorities by the GDG because scalp psoriasis affects a large proportion of patients and is typically managed in primary care. As with topicals used to treat other body sites, even if the unit costs of the interventions are quite modest,

the population affected is relatively large; therefore the health economic impact of any recommendation is likely to be substantial.

One cost-effectiveness analysis was identified in the published literature, but it had methodological limitations that called its conclusions into question. The analysis by Affleck[244] did not include all of the relevant comparators under consideration for the guideline, namely very potent corticosteroids. Furthermore, the treatment effects used in their analysis differed from those found in the NCGC clinical review and network meta-analysis, and this difference was considered likely to affect the conclusion of the analysis. Due to these methodological limitations, there was still substantial uncertainty as to which topical therapy or therapies represented the best value for NHS resources in the treatment of scalp psoriasis. In order to reduce this uncertainty, an original cost-effectiveness analysis was undertaken by the guideline health economist in collaboration with the GDG. Below is a summary of the analysis that was undertaken. For full details please see Appendix N.

8.9.2.1 Methods

An analysis was undertaken to evaluate the relative cost-effectiveness of different topical therapy sequences used in the treatment of individuals with moderate to severe scalp psoriasis. A Markov model was used to estimate 12-month costs and quality-adjusted life years (QALYs) from a current UK NHS and personal social services perspective. A 12-month time horizon was considered clinically relevant and sufficiently long enough to capture important costs and consequences of first-line treatment in primary care. Uncertainty was explored through probabilistic analysis and sensitivity analysis. The performance of alternative treatment sequences was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness.

The aim of the analysis was to identify the most cost-effective sequence of first, second and third line topical therapies for scalp psoriasis. It was important to model sequences given that most patients will commence treatment with one topical and then try others before moving on to more intensive treatments such as specialist applied topicals and/or systemic therapy. Table 74 presents the list of possible first, second and third line scalp treatments which may be combined in a sequence.

Table 74: Possible sequences of first, second and third line treatment

First line	Second line	Third line
Vitamin D or vitamin D analogue OD	Vitamin D or vitamin D analogue OD	Combined product containing calcipotriol monohydrate and betamethasone dipropionate OD
Vitamin D or vitamin D analogue BD	Vitamin D or vitamin D analogue BD	Very potent corticosteroid OD
Potent corticosteroid OD	Potent corticosteroid OD	Very potent corticosteroid BD
Potent corticosteroid BD	Potent corticosteroid BD	Coal tar polytherapy (Capasal)
TCF OD	TCF OD	Referral to specialist
Very potent corticosteroid OD	Very potent corticosteroid OD	
Very potent corticosteroid BD	Very potent corticosteroid BD	

The following conditions were placed on the sequences, ensuring that they represented logical clinical practice:

- Once daily treatment with a given topical would not come after a failure of twice daily treatment with the same topical;

- Once daily treatment with potent steroid or vitamin D or vitamin D analogue would not come after once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate;
- Once or twice daily treatment with potent corticosteroid would not come after once or twice daily with very potent corticosteroid.

Most comparators focus on evaluating a trial of three different treatments before referral for specialist review, but the GDG was also interested in whether earlier escalation of care might be more cost-effective. To test this, strategies have also been combined into two-treatment sequences with referral following a failure of second line treatment.

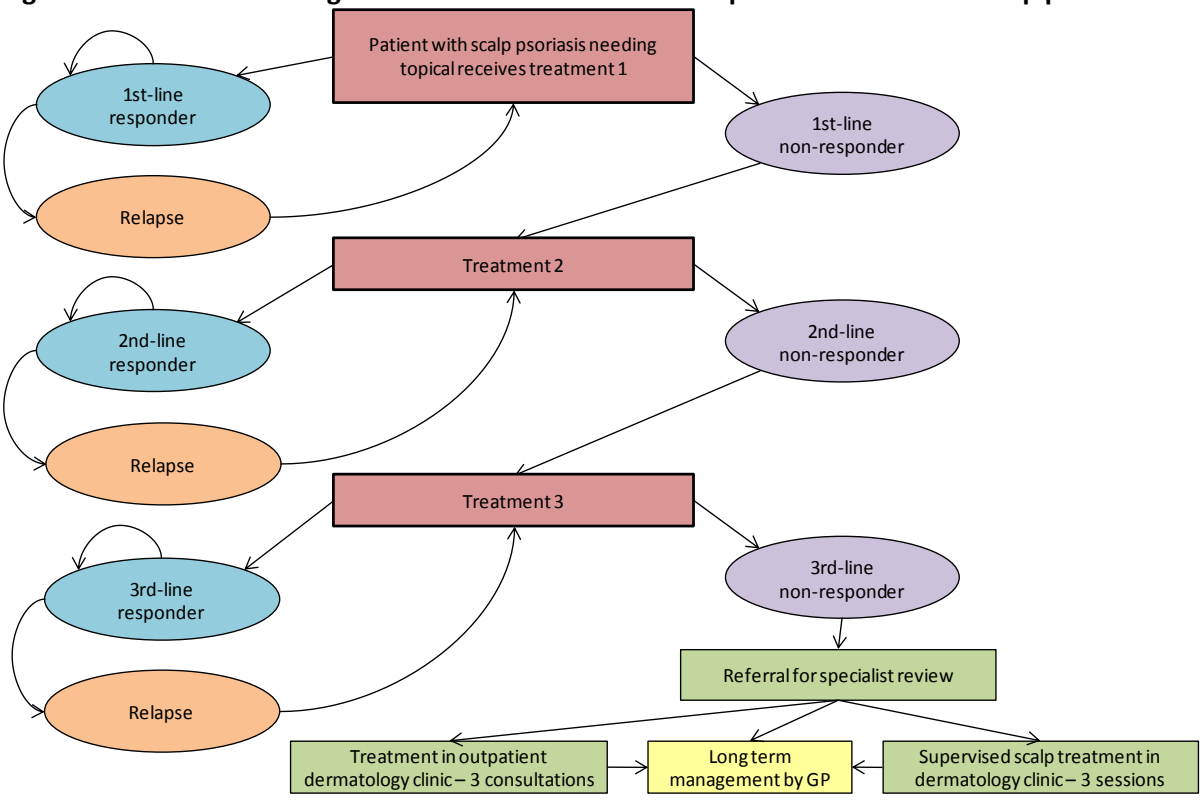
Due to the unacceptability coal tar as a routine treatment (strong and unpleasant odours), this treatment was reserved for third line treatment only. This reflects their current placement in primary care given the availability of more acceptable and effective topicals such as those being compared as first and second line topicals.

The structure of the model developed by the NCGC was adapted from the model developed by Affleck and colleagues[244] and was validated by the GDG as a reasonable reflection of current clinical practice. The Markov model and how patients move through the pathway is illustrated in Figure 7. Key model assumptions (these are discussed in more detail in the full write-up in Appendix N):

- All hypothetical patients commence treatment with a given topical and experience one of two outcomes after 4 or 8 weeks:
  - response (defined as clearance/near clearance of their scalp psoriasis) or
  - no response (defined as something less than clearance/near clearance of their scalp psoriasis).
- Patients who respond stop treatment and they either maintain response in the absence of treatment or they relapse.
  - Patients who relapse resume treatment with the same topical and again face a probability of responding or not responding.
- Patients who do not respond to a given topical after 8 weeks of treatment are assumed to return to their GP and receive a prescription for an alternative topical therapy.
- Patients can receive up to three different topical therapies before being referred by the GP to a specialist review in an outpatient dermatology clinic where second-line treatment options could be considered.
  - Some proportion of these referred patients will be kept on topical therapies, receive support and advice at the review consultation and be discharged back to their GP for long-term management.
  - Some will be treated by a specialist over 3 appointments in outpatient dermatology
  - The remaining proportion undergo a supervised scalp treatment with intensive topical therapy over the course of 3 dermatology day centre appointments:
    - If they respond to intensive topical therapy they are then discharged to their GP for long-term management.
    - If they do not respond to intensive topical therapy they continue to be managed by a specialist.

Movement between various health states is governed by transition probabilities, derived from the systematic review of clinical effectiveness data and network meta-analysis. Thirteen 4-week cycles were modelled, resulting in a 1-year time horizon for the analysis, with a half-cycle correction applied.

Figure 7: Patient flow diagram for the Markov model of topical treatments for scalp psoriasis



Model inputs were based on the clinical effectiveness review undertaken for the guideline, other published data and expert opinion where required. These are described in full in the technical report in Appendix N. All model inputs and assumptions were validated by the GDG.

8.9.242 Results

This analysis found that, given a NICE willingness-to-pay threshold of £20,000 per QALY gained, the most cost-effective strategy is likely to be one of starting with once daily potent corticosteroid and then escalating to twice daily very potent corticosteroid and then trying once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate if steroids alone are insufficient to induce clearance or near clearance. This conclusion was based on the comparison of mean costs and mean QALYs across 169 modelled sequences. Base case results for non-dominated and non-extendedly dominated strategies are presented in Table 75. By starting with twice daily very potent corticosteroid and moving on to once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate and then ultimately twice daily vitamin D or vitamin D analogue, 0.0004 QALYs could be gained, but for an additional £102 per year. This gives and ICER of £254,250 per QALY gained, which is not cost-effective at the NICE threshold.

Table 75: Incremental analysis of base case results – scalp psoriasis

Strategy (a)	Cost	Incrmntl Cost	Benefit (QALYs)	Incrmntl benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold (b)
PS OD - PS BD -	£145		0.77407			£15,337	18%

Strategy (a)	Cost	Incrmntl Cost	Benefit (QALYs)	Incrmntl benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold (b)
VPS BD							
PS OD - VPS BD - TCF OD	£156	£11	0.77486	0.00079	£14,430	£15,341	40%
VPS BD - TCF OD - Vit D BD	£258	£102	0.77526	0.0004	£254,250	£15,247	0%

(a) All sequences not presented here were ruled out through dominance (more costly and less effective than a strategy included in the table) or extended dominance (more costly and less effective than a mixture of two other strategies included in the table)

(b) Strategies not on the cost-effectiveness frontier but with second, fourth and fifth highest expected net benefits include PS OD – VPS OD – VPS BD, PS OD –V PS BD – Vit D OD and PS OD – VPS BD –Vit D BD, respectively.

Complete results for all 169comparators can be found in Appendix N. Overall, results of the analysis showed that the most effective and cost-effective strategies involved use of potent and very potent corticosteroids in all three lines of treatment.

Results of the analysis showed that a strategy of using vehicle gel or emollient with no active agent only was the most costly and least effective strategy, largely driven by the cost of referrals and specialist management for non-responders. Similarly, a strategy of prescribing coal tar polytherapy for ongoing management was only slightly more effective than continued use of vehicle gel and cost the third most of any treatment sequence. Under base case assumptions, strategies that included once or twice daily vitamin D or vitamin D analogue were not cost-effective regardless of where they came in a treatment sequence. This finding is driven by their relatively low rank in terms of effectiveness and their relatively high acquisition cost relative to potent and very potent corticosteroids. Two compound formulation product, although second most effective in the network meta-analysis, was not found to be cost-effective as a first or second line intervention. Like vitamin D or vitamin D analogues, its high unit cost compared to other cheaper and effective topicals makes it unlikely to represent reasonable value for NHS resources if offered before potent or very potent corticosteroids.

The probabilistic analysis indicates that there is a great deal of uncertainty as to which sequence is optimal (i.e. most cost-effective). No single sequence was most cost-effective at a £20,000 per QALY willingness to pay threshold in more than 40% of simulations; however, looking across strategies indicates that those starting with once daily potent corticosteroid were optimal in 84% of simulations. In 49% of all simulations, following once daily potent with twice daily very potent was optimal. In the remaining 16% of simulations, a sequence starting with either once or twice daily very potent corticosteroid was likely to be most cost-effective. This trend indicates that we can be reasonably confident that starting with once daily potent corticosteroid is going to bring the greatest benefit for resources used, and that moving to a very potent corticosteroid, either once or twice daily is likely to provide further benefit at reasonable extra cost.

A series of scenario analysis suggested that the conclusions from the base case are somewhat sensitive to changes in assumptions made.

Lower expected resource use for combined product containing calcipotriol monohydrate and betamethasone dipropionate

The base case of this analysis assumed that patients using combined product containing calcipotriol monohydrate and betamethasone dipropionate for 4 weeks would use approximate 71.4 g of

product. This estimate was based on the mean across five RCTs[228,229,232,233,242]. In a recent UK cost-utility analysis, Affleck and colleagues[244] assumed the 4-week quantity used to be 60 g. At this quantity, the unit cost of combined product containing calcipotriol monohydrate and betamethasone dipropionate is cut nearly in half. This value was used in a sensitivity analysis to explore how sensitivity the results were to this particular value.

The results suggest that the conclusions are insensitive to variation in this parameter. Here, as in the base case, the most cost-effective strategy is once daily potent corticosteroid followed by twice daily very potent corticosteroid and then once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate. The ICER comes down to £12,093 in this sensitivity analysis compared to £14,430 in the base case. Even at this reduced cost though, combined product containing calcipotriol monohydrate and betamethasone dipropionate does not represent better value for NHS resources than potent or very potent corticosteroids alone as a first-line strategy.

Scenario analyses – restricted comparators

The base case analysis put a few conditions on the way topicals could be sequences (see Table 74 in section 8.9.2.1. These did not restrict how potent and very potent corticosteroids were fit into treatment sequences. The GDG expressed concern that this lack of restrictions may not fully reflect the way these topicals are and should be used in general practice. They indicated that much more caution is and should be used when prescribing potent and very potent corticosteroids for both continuous and intermittent use. The GDG was also concerned that the analysis did not fully capture the safety risks associated with the use of these agents. In a stepwise fashion, various additional restrictions were placed on the use of these agents in each sequence.

In the first scenario, all strategies involving potent or very potent corticosteroids (including combined product containing calcipotriol monohydrate and betamethasone dipropionate) in all three lines of treatment were removed. The results confirmed the findings of the base case results in which once daily potent corticosteroid then twice daily very potent corticosteroid was found to be most cost-effective as first and second-line treatments. However, in this scenario no further steroid could be prescribed; therefore once daily vitamin D or vitamin D analogue was found to be the most cost-effective third line treatment.

In the second scenario, no sequence could include the consecutive use of potent or very potent corticosteroid, including as part of combined product containing calcipotriol monohydrate and betamethasone dipropionate. The results again showed the likely cost-effectiveness of strategies including potent and very potent corticosteroids. Here, starting with once daily potent corticosteroids and then moving to once daily vitamin D or vitamin D analogue and then twice daily very potent corticosteroids was least costly and second most effective. Starting the sequence with twice daily very potent corticosteroid and ending with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate generated 0.00118 more QALYs, but at an additional cost of £45.90 per year. The resulting ICER (£38,898) is thus over the £20,000 per QALY threshold.

In the third scenario, twice daily application of very potent corticosteroid could not precede once daily application. Under this condition, a strategy of starting with once daily potent corticosteroid and then escalating up to once daily very potent corticosteroid and then finally up to twice daily very potent corticosteroid was most likely to be cost-effective. Starting with once and then twice daily very potent corticosteroid and ending with once daily TCF produce produced an additional 0.00012 QALYs, but at an additional cost of £52.60 (ICER=£438,333).

If these conditions are combined with those outlined in scenarios 1 and 2, then the optimal sequence is to start with once daily very potent corticosteroid then move to once daily vitamin D or vitamin D analogue and finally to twice daily very potent corticosteroid. A strategy of starting with once daily

potent corticosteroids, followed by once daily vitamin D or vitamin D analogue and then ended with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate generates an additional 0.00002 QALYs, but at a cost of £31.10 (ICER=£1.56 million) making it unlikely to be cost-effective by the NICE willingness to pay threshold.

In addition to the concerns raised about the safety of potent and very potent corticosteroids, the GDG raised the issue of cosmetic acceptability and its importance in the treatment of scalp psoriasis. In particular, they voiced a strong preference for once daily application, stating that few patients would be willing or interested in applying topicals to their scalp more than once a day, specifically at night. On that basis, modelled comparators were restricted in a stepwise fashion.

In the first scenario, twice daily strategies were reserved for third line treatment following failure of at least two once daily strategies. If steroids could be offered in all three lines of treatment, then the optimal sequence was to start with once daily potent corticosteroid, move up to once daily very potent corticosteroid and then escalate to twice daily very potent corticosteroid if necessary. If one is looking to avoid using very potent corticosteroids first or second line in the sequence, then the next most cost-effective sequence under these conditions was once daily vitamin D or vitamin D analogue as a second option following initial once daily potent corticosteroid, and still ending with twice daily very potent corticosteroid would still be the most cost-effective third line topical. Replacing vitamin D or vitamin D analogue with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate in this sequence is expected to yield an additional 0.00066 QALYs for an extra £36.20 per year (ICER=£54,848).

In a second scenario, all twice daily strategies were removed and only sequences of once daily treatments were included. If steroids could be offered anywhere in the sequence, then the most cost-effective strategy was to start with potent corticosteroids, move up to very potent corticosteroids and then try combined product containing calcipotriol monohydrate and betamethasone dipropionate if both steroids alone have failed. Moving the combined product containing calcipotriol monohydrate and betamethasone dipropionate from the end of the sequence to the beginning is expected to produce an additional 0.00013 QALYs at an additional cost of £112 per year (ICER=£862,308). If one wishes to avoid consecutive use of steroids, then the optimal strategy is to start with potent steroids, then switch to vitamin D or vitamin D analogues and end with very potent corticosteroids. Replacing very potent corticosteroids with the combined product containing calcipotriol monohydrate and betamethasone dipropionate in this sequence generates 0.00032 more QALYs, but with an ICER too high to be considered cost-effective (ICER=£64,375).

8.9.2.3 Interpretation and limitations

In assessing the relative cost-effectiveness of alternative topical therapies in patients with moderate to severe scalp psoriasis limited evidence was available from the published economic literature. The evidence that was identified and included in the health economic review had potentially serious limitations and therefore the GDG considered it a priority to undertake original evaluation for the guideline in order to inform recommendations.

Original decision modelling undertaken for the guideline showed that there were relatively small differences in terms of benefit between 169 different topical sequences, but the differences in terms of cost were quite substantial. Based on the mean costs and benefits, the analysis suggests that initial treatment with once daily potent corticosteroid followed by twice daily very potent corticosteroid and then once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate if steroids alone are insufficient to induce clearance or near clearance is likely to represent the most cost-effective sequence for moderate to severe scalp psoriasis. Uncertainties in the analysis were explored through sensitivity analysis which showed that in some scenarios in which restrictions were placed on the comparators

- Once daily vitamin D or vitamin D analogue might be cost-effective second or third in the sequence, after trials of potent or very potent corticosteroids
- The combined product containing calcipotriol monohydrate and betamethasone dipropionate is likely to be cost-effective third in sequences, after potent and very potent corticosteroids and when only once daily applications of topicals are being considered

In general, sequences ending with once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate were slightly more effective than the same sequence ending with alternatives such as vitamin D or vitamin D analogue or potent corticosteroid; however, the very modest additional benefit (<0.0007, dependent on comparator) would only be considered potentially cost-effective if willingness to pay thresholds were between £40,000 and £2 million per QALY gained. If, however, the amount of combined product containing calcipotriol monohydrate and betamethasone dipropionate used by patients is less than reported in the clinical trial evidence, such that a single 60 g pack is needed for 4 weeks, then the combined product containing calcipotriol monohydrate and betamethasone dipropionate may be more cost-effective earlier in a given sequence.

The analysis has several limitations which were considered carefully by the GDG. Firstly, the analysis evaluates treatment sequences even though the available trial data compares single topicals head to head without sequencing. In order to apply the treatment effects within the sequencing model, we assumed that treatment effects were independent. That is, we assumed the effectiveness of the combined product containing calcipotriol monohydrate and betamethasone dipropionate as a second or third line topical was equal to its effectiveness as a first line agent and that this was true regardless of other topicals it may follow. The GDG did not believe this to be a significant limitation given that the patients included in the overwhelming majority of RCTs were reported to have psoriasis for longer than 5 years, during which they can be assumed to have previously tried, succeeded and/or failed various topical treatments.

The analysis only captured the efficacy of topicals and did not capture the costs or consequences of adverse events. Although the RCT evidence on adverse events was sparse, the GDG is conscious of the risks associated with the long-term use of potent and very potent corticosteroids. They carefully considered whether the added effect in terms of clearance was worth the potential risks of adverse effects.

The model was also focused on the induction of disease clearance as opposed to the maintenance of clearance. No trials focusing on maintenance were identified in the clinical evidence review and therefore no evidence was available for use in the economic model.

The model also takes a relatively short time horizon considering that psoriasis of the scalp is a chronic, long term condition for which patients may take up treatment intermittently for many years of their lives. Frequency and severity of relapse, selection for and speed of onward referral, methods of self-management and long-term safety are all issues inadequately addressed in the evidence base and therefore translate into limitations of the economic analysis.

This analysis of the treatment of psoriasis of the scalp is distinct from the analysis of the treatment of scalp of the trunk and/or limbs largely because it is based on a different evidence base and as such has given rise to site-specific recommendations. In clinical practice, health care professionals are likely to see patients who are dealing with psoriasis at a variety of sites, including their face and flexures. It is quite possible that health care professionals will need to prescribe different topicals for different sites, meaning that patients may have several different agents at a time. Indeed, even if they are using the same product (i.e. potent corticosteroid) on different sites, they may be prescribed different formulations for each site (i.e. creams or ointments for the trunk and limbs; gels or foams for the scalp). It would be simpler to prescribe one single treatment for all sites, but as the

clinical and cost-effectiveness has shown, such an approach may not represent the most effective or efficient use of NHS resources.

8.9.234 Comparison with published studies

The findings from the NCGC original economic analysis are quite different from the results of the most similar published study by Affleck and colleagues[244]. Affleck and colleagues found a sequence starting with twice daily potent corticosteroids followed by concurrent treatment with vitamin D or vitamin D analogue and potent corticosteroid corticosteroids (one applied in the morning and one in the evening) and then once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate to be most cost-effective. Although the analysis appears to have been executed well, the included comparators and the estimates of effect and resource use had limitations which called the conclusions of the analysis into question.

The biggest differences in the results of the NCGC analysis presented here and the analysis undertaken by Affleck has to do with the comparators included, namely the inclusion/exclusion of very potent corticosteroids. The NCGC analysis included very potent corticosteroids as the network meta-analysis demonstrated them to be highly efficacious in the short term treatment of psoriasis of the scalp. The GDG confirmed that although very potent corticosteroids are not normal management for the treatment of the trunks and limbs, they constitute a reasonable, short-term option for treating the scalp.

The second key difference between the analyses relates to the relative treatment effects used. Affleck and colleagues derived their treatment effects from an adjusted indirect comparison[245], which, when compared to the NCGC network meta-analysis, appears to have overestimated the effectiveness of the combined product containing calcipotriol monohydrate and betamethasone dipropionate compared to other topicals. For example, in their analysis the combined product containing calcipotriol monohydrate and betamethasone dipropionate was found to be 2.45 times more likely to induce response than once daily calcipotriol (RR=2.45, 95% CI: 1.84 to 3.27). The NCGC network meta-analysis found the risk ratio to be lower, around 1.614. This translates into an absolute risk difference between the two comparators of 35.54% using Affleck's estimates and 27.66% using the NCGC estimates. Differences such as these add up when synthesised in economic models and could lead to biased conclusions.

In addition, the estimate they used for quantity of combined product containing calcipotriol monohydrate and betamethasone dipropionate used per 4-week treatment period was 60 g, compared to the estimate used in the NCGC analysis 71.4 g. Based on these estimates of resource use, the NCGC analysis assumes 4 weeks of combined product containing calcipotriol monohydrate and betamethasone dipropionate costs £31.29 more than Affleck and colleagues did. We performed a sensitivity analysis in which we assumed the same quantity of combined product containing calcipotriol monohydrate and betamethasone dipropionate used by Affleck and colleagues (i.e. 60 g, £36.50). The ICER for combined product containing calcipotriol monohydrate and betamethasone dipropionate as a third line treatment improved compared to the base case (£19,286 vs £44,286), making it potentially cost-effective given the NICE willingness to pay threshold. However, there remains a great deal of uncertainty in this conclusion.

One thing that Affleck and colleagues were able to capture that the NCGC analysis was not had to do with the potential disutilities associated with adverse events. They included these in their base case, and unfortunately did not report a sensitivity analysis wherein they were removed altogether with which to compare. However, the authors did state that variation in the incidence of adverse events, upwards and downwards, did not change the conclusions of their analysis.

8.9.215 Evidence statements

- One directly applicable study with potentially serious limitations found that a sequence of potent corticosteroid followed by concurrent vitamin D or vitamin D analogue and potent corticosteroid corticosteroids (one applied in the morning and one in the evening) and followed by the combined product containing calcipotriol monohydrate and betamethasone dipropionate to be the most cost-effective strategy to treat chronic scalp psoriasis.
- One directly applicable study with potentially serious limitations found that treatment sequences that do not include combined or concurrent vitamin D or vitamin D analogue and potent corticosteroids (one applied in the morning and one in the evening) are among the least effective and most costly in the treatment of chronic scalp psoriasis.
- New economic analysis from a current UK NHS and PSS perspective comparing 169 different sequences of topical therapies found sequences beginning with once daily potent corticosteroids to offer the best value for NHS resource in the treatment of patients with moderate to severe scalp psoriasis. This conclusion was robust to the majority of sensitivity analyses undertaken.
    - Choice of second and third line treatments was more uncertain, but very potent corticosteroids, once or twice daily, were generally shown to be most cost effective followed by once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate. This conclusion was sensitive to alternative assumptions regarding suitability and acceptability of certain comparators.
        - Sensitivity analyses in which continuous or consecutive use of topicals containing steroids was restricted found that once daily vitamin D or vitamin D analogue may be cost-effective as second or third line treatment in sequences with potent and very potent corticosteroids.
        - Sensitivity analyses in which very potent corticosteroids were reserved for third line treatment showed that once daily vitamin D or vitamin D analogue or once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate may offer the best and second best value for NHS resources, respectively.
        - Sensitivity analyses in which only once daily applications were considered found that initial treatment with potent steroids was optimal, followed by either very potent corticosteroid and then combined product containing calcipotriol monohydrate and betamethasone dipropionate if steroids could be used continuously or followed by vitamin D or vitamin D analogue and very potent corticosteroid if continued use of steroids was to be avoided.

8.10 Topical therapies for high impact or difficult to treat sites: face and flexures (including genitals)

There were 3 studies that addressed the efficacy and safety of topical treatments for psoriasis affecting the face and/or flexures.

- One study[238] combined people treated for affected skin on the face and intertrigenous areas (proportions not given)
- One study[223] included only inverse/flexural sites
- One study[224] combined people treated for affected skin on the face and genitofemoral areas (90% had lesions on the face and 10% on the genitofemoral sites)

8.10.1 Tacrolimus vs. placebo

8.10.1.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tacrolimus	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – Tacrolimus BD (follow-up 8 weeks)											
1 Lebwohl 2004	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/112 (65.2%)	17/55 (30.9%)	RR 2.11 (1.39 to 3.2)	343 more per 1000 (from 121 more to 680 more)	⊕⊕OO LOW
Withdrawals due to adverse events – Tacrolimus BD (follow-up 8 weeks)											
1 Lebwohl 2004	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	The adverse event was not at the treatment site	0/98 (0%)	1/40 (2.5%)	RR 0.14 (0.01 to 3.32)	22 fewer per 1000 (from 25 fewer to 58 more)	⊕OOO VERY LOW
Withdrawals due to lack of efficacy – Tacrolimus BD (follow-up 8 weeks)											
1 Lebwohl 2004	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/98 (0%)	6/45 (13.3%)	RR 0.04 (0 to 0.62)	128 fewer per 1000 (from 51 fewer to 133 fewer)	⊕⊕OO LOW

(a) Unclear allocation concealment and blinding; high dropout rate in placebo group (29.1% vs 12.5% in tacrolimus group)

(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.10.122 Evidence statements

In people with chronic plaque psoriasis affecting the face and/or intertrigenous areas, tacrolimus twice daily was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [1 study; 167 participants; low quality evidence][238]
- Withdrawal due to lack of efficacy at 8 weeks [1 study; 143 participants; low quality evidence][238]

In people with chronic plaque psoriasis affecting the face and/or intertrigenous areas, there was no statistically significantly difference between tacrolimus twice daily and placebo for:

- Withdrawal due to adverse events at 8 weeks [1 study; 138 participants; very low quality evidence][238]

8.10.22 Pimecrolimus vs. placebo

8.10.231 5.2.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pimecrolimus	Placebo	Relative (95% CI)	Absolute	
Investigator's assessment (clear/nearly clear) – Pimecrolimus BD (follow-up 8 weeks)											
1 Gribetz 2004	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/28 (71.4%)	6/29 (20.7%)	RR 3.45 (1.63 to 7.31)	507 more per 1000 (from 130 more to 1000 more)	⊕⊕⊕⊕ HIGH
Withdrawals due to adverse events – Pimecrolimus BD (follow-up 8 weeks)											
1 Gribetz 2004	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/26 (0%)	0/25 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH

Withdrawals due to lack of efficacy – Pimecrolimus BD (follow-up 8 weeks)											
1 Gribetz 2004	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/27 (3.7%)	2/27 (7.4%)	RR 0.50 (0.05 to 5.19)	37 fewer per 1000 (from 70 fewer to 310 more)	⊕⊕OO LOW
Skin atrophy – Pimecrolimus BD (follow-up 8 weeks)											
1 Gribetz 2004	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	0/29 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH

(a) Higher drop-out in placebo group (13.8% vs 7.1% in pimecrolimus group) but rates acceptable in both groups

(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

8.10.232 Evidence statements

In people with chronic plaque psoriasis affecting the flexural areas, pimecrolimus twice daily was statistically significantly better than placebo for:

- Investigator's assessment (clear/nearly clear) at 8 weeks [1 study; 57 participants; high quality evidence][223]

In people with chronic plaque psoriasis affecting the flexural areas, there were no events with either pimecrolimus twice daily or placebo for:

- Withdrawal due to adverse events at 8 weeks [1 study; 51 participants; high quality evidence][223]
- Skin atrophy at 8 weeks [1 study; 57 participants; high quality evidence][223]

In people with chronic plaque psoriasis affecting the flexural areas, there was no statistically significant difference between pimecrolimus twice daily and placebo for:

- Withdrawal due to lack of efficacy at 8 weeks [1 study; 54 participants; low quality evidence][223]

8.10.23 Tacrolimus vs. vitamin D or vitamin D analogue

8.10.331 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Tacrolimus	Vitamin D or	Relative	Absolute	

studies		bias				considerations		vitamin D analogue	(95% CI)		
Investigator's assessment (clear/nearly clear) – Tacrolimus BD vs calcitriol BD (follow-up 6 weeks)											
1 Liao 2007	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	15/25 (60%)	8/24 (33.3%)	RR 1.8 (0.94 to 3.45)	267 more per 1000 (from 20 fewer to 817 more)	⊕⊕OO LOW
Withdrawals due to adverse events – Tacrolimus BD vs calcitriol BD (follow-up 6 weeks)											
1 Liao 2007	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/25 (0%)	0/21 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Withdrawals due to lack of efficacy – Tacrolimus BD vs calcitriol BD (follow-up 6 weeks)											
1 Liao 2007	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/25 (0%)	0/21 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE

(a) Unclear allocation concealment and not matched at baseline for sex or disease severity (less severe and fewer men in tacrolimus group); higher dropout rate in calcipotriol group (12% vs 0% on tacrolimus)

(b) Confidence interval ranges from clinically important effect to no effect

In people with chronic plaque psoriasis affecting the face and/or genitofemoral areas, there were no events with either tacrolimus twice daily or vitamin D (calcitriol twice daily) for:

- Withdrawal due to adverse events at 6 weeks [1 study; 46 participants; moderate quality evidence][224]
- Withdrawal due lack of efficacy at 6 weeks [1 study; 46 participants; moderate quality evidence][224]

In people with chronic plaque psoriasis affecting the face and/or genitofemoral areas, there was no statistically significant difference between tacrolimus twice daily and vitamin D (calcitriol twice daily) for:

- Investigator's assessment (clear/nearly clear) at 6 weeks [1 study; 49 participants; low quality evidence][224]

8.11 Face and flexures (including genitals) – time to remission/maximum effect

8.11.1 Tacrolimus

8.11.1.1 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tacrolimus BD		
Mean time to maximum response (PGA) (follow-up 57 days)									
1 Lebwohl 2004	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Tacrolimus 0.1% 112	Patients achieving excellent improvement or clearing Day 8: 24.8% Day 57: 66.7%	⊕⊕OO LOW
Mean time to maximum response (PGA) (follow-up 57 days)									
1 Lebwohl 2004	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	Tacrolimus 0.1% 112	Based on graphical representation of the % with excellent improvement or clearing the majority of those who achieved success did so by day 29, with a small decrease in % to day 43 but a further increase of <5% between days 29 and 57	⊕OOO VERY LOW
Mean time to maximum response (PGA) (follow-up 6 weeks)									
1 Liao 2007	observational studies[a]	no serious risk of bias[b]	no serious inconsistency	serious[d]	very serious[c]	none	Tacrolimus 0.03% 25	Graphical representation of % clear or nearly clear over time demonstrated that maximum effect was reached not reached by week 6	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm
(b) Unclear allocation concealment may have biased patient selection for this intervention
(c) Interpreted from graphical representation
(d) Incorrect outcome measure

8.11.112 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical tacrolimus (no statistical analysis could be performed).

In people with face/flexural psoriasis, the time to remission when using tacrolimus varied between studies:

- Proportion achieving remission on tacrolimus 0.1% by 57 days was 66.7% [1 study; 112 participants; low quality evidence][238]
- Of those who achieved remission on tacrolimus 0.1% by the end of the trial, 37.2% had responded by day 8 based on investigators assessment [1 study; 112 participants; low quality evidence][238]
- Mean time to remission on tacrolimus 0.1% on PGA showed that a maximum effect was reached by week 4 [1 study; 112 participants; very low quality evidence][238]
- Mean time to maximum response based on tacrolimus 0.03% on PGA showed that a maximum effect was not reached by week 4 [1 study; 25 participants; very low quality evidence][224]

8.11.123 Summary

The evidence suggests that maximum response to tacrolimus 0.1% is achieved by 4 weeks of treatment, but maximum response is later when using a lower concentration[224,238].

8.11.52 Pimecrolimus

8.11.261 Evidence profile

Quality assessment							No of patients	Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pimecrolimus 1% BD		
Time-to-clear/nearly clear (follow-up 8 weeks)									
1 Gribetz 2004	observational studies[1]	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	Percentage of patients clear or almost clear Baseline: 0% Day 3: 14.3%	⊕⊕OO LOW

								Day 7: 35.7% Week 2: 53.6% Week 4: 64.3% Week 6: 67.9% Week 8: 71.4%	

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the comparator arm

(b) Unclear allocation concealment may have biased patient selection for this intervention

8.11.2.2 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for topical pimecrolimus (no statistical analysis could be performed).

In people with flexural psoriasis, the time to remission when using pimecrolimus was as follows:

- Proportion achieving remission by 8 weeks was 71.4% [1 study; 28 participants; low quality evidence][223]
- The continued increase in responders between 6 and 8 weeks was 3.5% [1 study; 28 participants; low quality evidence][223]
- Some people (35.7%) achieved remission by 1 week [1 study; 28 participants; low quality evidence][223]
- Of those who achieved remission by the end of the trial (8 weeks), 75.1% had responded by week 2, 90.1% by week 4 and 95.1% by week 6 based on investigators assessment [1 study; 28 participants; low quality evidence][223]

8.11.2.3 Summary

The evidence suggests that maximum response may be achieved by 8 weeks, with the continued response rate increasing only slightly between weeks 6 and 8 [223]. However, the majority of those who will respond within 8 weeks had done so by week 4.

8.11.3 Cost effectiveness evidence – face and flexures (including genitals)

No relevant studies were identified. In the absence of recent UK cost-effectiveness analysis, relevant unit costs were sourced to aid consideration of cost effectiveness (Table 76).

Table 76: Costs of medications for face and flexures (including genitals)

Item	Cost	Notes
Tacrolimus	0.03%, net price 30g=£21.60, 60 g=£39.40	Protopic® (Astrellas), Ointment
Pimecrolimus	1%, net price 30g = £19.69, 60g = £37.41, 100g = £59.07	Elidel® (Novartis), Cream
Moderately potent corticosteroid	Hydrocortisone, net price 30g=£2.38, 100g = £7.03	Alphaderm® (Alliance), Cream
	Hydrocortisone, net price 100g = £8.76	Calmurid HC® (Gladerma), Cream
	Hydrocortisone, net price 30g = £2.38, 100g = £7.03	Hydromol HC Intensive® (Alliane), Cream
	Alclometasone dipropionate, net price 50g = £2.68	Modrasone® (TEVA UK), Cream or ointment
	Betamethasone (as valerate), net price 100g = £3.15	Betnovate-RD® (GSK), Cream or ointment
	Clobetasone butyrate, net price 30g = £1.86, 100g = £5.44	Eumovate® (GSK), Cream or ointment
	Fluocinolone Acetonide, net price 50g = £4.40	Synalar 1 in 4 Dilution® (GP Pharma), Cream or ointment

Source/Note: *BNF 62*[246]

8.12 Recommendations and link to evidence

Recommendations on topical therapy for scalp psoriasis	**46. Offer a potent corticosteroid[p] applied once daily for a maximum period of 8 weeks as initial treatment for people with scalp psoriasis. Choose a low-cost preparation.** **47. Show people with scalp psoriasis how to safely apply**

p At the time of publication (May 2012), potent corticosteroids had UK marketing authorisation for this indication in adults, but in children licensed use was limited to 5 days and not for children under 1 year of age. Informed consent should be obtained and documented.

corticosteroid topical treatment.

48. If treatment with a potent corticosteroid[q] does not result in clearance, near clearance or satisfactory control of scalp psoriasis after 4 weeks consider:

- **a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or**
- **topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before further application of the potent corticosteroid.**

If the response remains unsatisfactory after a further 4 weeks of treatment offer:

- **a combined product containing calcipotriol monohydrate and betamethasone dipropionate[r] applied once daily for up to 8 weeks or**
- **vitamin D or a vitamin D analogue[s] applied once daily.**

49. If continuous treatment with either a combined product containing calcipotriol monohydrate and betamethasone dipropionate applied once daily or vitamin D or a vitamin D analogue applied daily for up to 8 weeks does not result in clearance, near clearance or satisfactory control of scalp psoriasis offer:

- **a very potent corticosteroid applied up to twice daily for 2 weeks (up to a maximum of 4 weeks) for adults only or**
- **coal tar applied once or twice daily or**
- **referral to a specialist for additional support with topical applications and/or advice on alternative treatment options.**

50. Consider topical vitamin D or a vitamin D analogue[t] alone for the treatment of scalp psoriasis only in people who:

- **are intolerant to or cannot use topical corticosteroids at this site or**
- **have mild-to-moderate scalp psoriasis.**

51. Do not offer coal tar-based shampoos alone for the treatment of plaque-type scalp psoriasis.

q At the time of publication (May 2012), potent corticosteroids had UK marketing authorisation for this indication in adults, but in children licensed use was limited to 5 days and not for children under 1 year of age. Informed consent should be obtained and documented

r At the time of publication (May 2012), combined product containing calcipotriol monohydrate and betamethasone dipropionate did not have UK marketing authorisation for this indication in children. Informed consent should be obtained and documented.

s At the time of publication (May 2012), calcitriol and tacalcitol did not have UK marketing authorisation for this indication in children. Calcipotriol should be used in children. Informed consent should be obtained and documented.

t At the time of publication (May 2012), calcitriol and tacalcitol did not have UK marketing authorisation for this indication in children. Calcipotriol should be used in children. Informed consent should be obtained and documented.

	52. Do not use very potent corticosteroids for scalp psoriasis in children.
Recommendationd on topical therapy for psoriasis of the face, flexures and genitals	**53. Offer a short-term mild or moderate potency corticosteroid[u] applied once or twice daily (for a maximum of 2 weeks) to people with psoriasis of the face, flexures or genitals.** **54. Be aware that the face, flexures and genitals are particularly vulnerable to steroid atrophy and that corticosteroids should only be used for short-term treatment of psoriasis (1–2 weeks per month). Explain the risks to people undergoing this treatment and how to minimise them** **55. For people with psoriasis of the face, flexures or genitals who show an unsatisfactory response to, or require ongoing continuous treatment with, short-term moderate potency corticosteroids to maintain control, offer a calcineurin inhibitor[v] applied twice daily for 4 weeks. Calcineurin inhibitors should be initiated by healthcare professionals with expertise in treating psoriasis.** **56. Do not use very potent corticosteroids in children.** **57. When prescribing topical agents at facial, flexural and genital sites take into account that they may cause irritation and inform people undergoing treatment of these risks and how to minimise them.**
Future research recommendations	None for topicals.
Relative values of different outcomes	The relative values of the different outcomes for scalp, face and flexural (including genital) sites are the same as for trunk and limbs. • Clear/nearly clear (investigator) • Clear/nearly clear (patient) • % change in PASI • Duration of remission • Withdrawal due to toxicity • Withdrawal due to lack of efficacy • Skin atrophy Based on the results from the pairwise and network meta-analyses and the health economic model the GDG decided to recommend potent corticosteroids as the first topical intervention, followed by very potent steroids if this failed, as this was the most cost-effective option based on the investigator and patient assessment of achieving clear or nearly clear status. There was no clinically significant difference between

[u] At the time of publication (October 2012), moderate potency corticosteroids did not have UK marketing authorisation for this indication in adults or children. Informed consent should be obtained and documented.
[v] At the time of publication (October 2012), calcineurin inhibitors did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

	most interventions in terms of withdrawal due to toxicity and skin atrophy as the absolute numbers were low and clear evidence regarding duration of remission was lacking. It was also noted that the pair-wise comparison of the combined product containing calcipotriol monohydrate and betamethasone dipropionate compared to potent steroid alone (applied once daily for the scalp) did not show a clinically significant difference in efficacy, unlike for this comparison for treatment of the trunk and/or limbs.
Trade off between clinical benefits and harms	As with the use of corticosteroids on the trunk and limbs, the efficacy, time to clearance and cosmetic acceptability were felt to outweigh the potential risks of corticosteroids for treatment of the scalp. The GDG discussed the data showing that of those who respond by 8 weeks to potent corticosteroid treatment, approximately 84% had done so by 4 weeks. Therefore, it was agreed to consider different formulations and topical agents to remove scale if treatment had not been successful by 4 weeks. The GDG were more cautious when considering this trade off in favour of corticosteroids at face and flexural sites as risks of skin atrophy are higher. The GDG considered that only mild, or if necessary moderate potency corticosteroid could be justified. Calcineurin inhibitors whilst effective are unlicensed for psoriasis. The GDG considered that given the paucity of other options, the impact psoriasis has on these sites and also that these agents are licensed and widely used in eczema, they could be recommended following specialist advice. The GDG noted that, unlike at the trunk and limbs, from the scalp data there was a non-significant trend towards once daily application of a given topical to be more effective than twice daily application for all agents except very potent corticosteroids. This was in line with clinical experience that twice daily scalp treatments are not favoured by patients often resulting in poor adherence. Therefore, to optimise outcomes once daily application was recommended where possible as well as emphasising the importance of using the correct formulation and removal of adherent scale, which is particularly important when treating scalp psoriasis. When considering clinically appropriate sequences of treatment for scalp psoriasis the GDG agreed that starting with a very potent corticosteroid as the first topical intervention would be an inappropriately aggressive strategy
Economic considerations	The GDG relied on a variety of sources in their consideration of the costs and benefits of alternative topical therapies in the treatment of patients with scalp psoriasis. Limited evidence, both in terms of quantity and quality, was identified in the published literature. One study showed that starting with twice daily betamethasone valerate (potent corticosteroid) followed by concurrent (one applied in the morning and one in the evening) treatment with betamethasone dipropionate (potent corticosteroid) and calcipotriol (vitamin D analogue) and then once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate to be the most cost-

effective treatment sequence. Due to limitations of the study, the GDG remained uncertain about the robustness of these conclusions.

Original decision modelling was undertaken for the guideline and showed that there were relatively small differences in terms of benefit between different topical sequences for scalp psoriasis, but large differences in terms of cost. Based on the mean costs and benefits of 169 compared sequences, the analysis found that initial treatment with twice daily very potent corticosteroids is likely to offer the best value for NHS resource. The GDG was concerned that twice daily very potent corticosteroid, although most effective and cost-effective, is quite an aggressive initial strategy and carries greater risk of steroid-related adverse events, which were not captured by the model. Furthermore, the GDG noted strong patient preference for once daily applications due to the messiness, inconvenience and cosmetic acceptability of topicals applied to the scalp. Therefore the GDG chose not to recommend twice daily very potent steroids as either the first or second-line treatment. It was considered appropriate as third-line treatment, as the number of patients exposed to the risks would be fewer but the need for efficacy more urgent.

Of the remaining strategies, the two most cost-effective strategy were:

- 1st line – once daily potent corticosteroid; 2nd line - once daily vitamin D or vitamin D analogue ; 3rd line – twice daily very potent corticosteroid
- 1st line – once daily potent corticosteroid; 2nd line - once daily combined product containing calcipotriol monohydrate and betamethasone dipropionate (potent corticosteroid and vitamin D or vitamin D analogue) ; 3rd line – twice daily very potent corticosteroid

Where a less aggressive 3rd line treatment is required, once daily very potent steroid or coal tar are alternatives, which are cost-effective compared to referral.

The analysis also considered the cost-effectiveness of coal tar polytherapy (Capasal® shampoo) relative to other topicals in the treatment of scalp psoriasis. Coal tar based shampoo was only slightly more effective that placebo/vehicle scalp solution and far less effective than other topicals. In the model, this meant that more patients ended up failing treatment in primary care and being referred onward for specialist consultations and treatments, thus making the true costs to the NHS of treatment with coal tar shampoos much higher than the acquisition cost alone. The GDG was aware that coal tar based shampoos are regularly prescribed in primary care for treatment of scalp psoriasis and agreed that based on the evidence of clinical and cost-effectiveness that they are not optimal for the treatment of scalp psoriasis. In order to ensure more efficient use of NHS resources, they considered it important to discourage GPs from using this particular treatment modality.

No economic evidence was available to inform the GDG on the relative cost-effectiveness of topicals in the treatment of psoriasis at sites such

	as the face and flexures. Given the cost-effectiveness of corticosteroids in the treatment of psoriasis of the trunk, limbs and scalp, the GDG concluded that corticosteroids were likely to represent good value for money in the treatment of psoriasis of the face and flexures, if side-effects are manageable. However, they noted the substantial risk of skin atrophy associated with corticosteroid use at these sites, and thus concluded that neither potent nor very potent corticosteroids were safe or appropriate. In the absence of clinical and economic evidence, the GDG relied on their clinical experience with mild and moderate potency corticosteroids. They concluded that their low acquisition cost was very likely to be justified by the benefits gained compared to alternatives. Calcineurin inhibitors are more costly than moderate potency corticosteroids and are not licensed for the treatment of psoriasis. The GDG considered that they may represent good value for NHS resources if continuous treatment is required (and thus the risk of steroid-associated side effects is higher) or if moderate potency corticosteroids fail to bring about the desired level of response.
Quality of evidence	**All studies** The majority of the data on withdrawals (except withdrawals due to lack of efficacy for the placebo comparisons) and skin atrophy across all comparisons showed low event rates that gave very imprecise relative estimates, but in absolute terms demonstrated precise evidence of no clinically relevant difference between the interventions because the numbers involved were so low. Even in cases where there was a statistically significant difference in the interventions, such as withdrawals due to adverse events in the comparison of potent corticosteroids and placebo, in absolute terms there was no clinically significant difference between the interventions. The study limitations regarding steroid atrophy discussed in relation to trunk and limbs (see 7.4.4) also apply to high impact and difficult to treat sites. There was a lack of information regarding the duration of remission/time-to-relapse, which was only reported in 3 studies (Poulin 2010, Klaber 1994 and Kragballe 2009). While there was an overall trend that the relapse rate was higher following use of preparations including potent steroids compared with vitamin D or vitamin D analogues the different definitions of relapse and time-points of assessment made it difficult to assimilate the data. **Scalp psoriasis** • **Vitamin D or vitamin D analogues vs placebo:** There was heterogeneity between two studies (Jemec 2008 and Green 1994) included in the comparison of vitamin D or vitamin D analogues vs. placebo for scalp psoriasis for the outcome of investigator's assessment of achieving clear or nearly clear which wasn't explained by pre-defined subgroups but may have been due to a higher risk of bias in the Green 1994 study. Nevertheless, both studies suggest that vitamin D or vitamin D analogues are clinically beneficial in terms of achieving clearance or near clearance compared with placebo treatment. It was noted that some patients prefer the

solution, as it does not make the hair greasy, which the gel does.

- **Potent corticosteroid vs placebo:** One study (Franz 1999) investigating potent corticosteroid vs. placebo on the scalp included two experimental arms with different formulations of active treatment. Although it was not within the review protocol to investigate differences in formulation the GDG noted that a statistically significant difference was demonstrated between the foam and lotion formulations of betamethasone valerate (foam = 72% response, lotion = 47% response on investigator's assessment; results for the patient's assessment were similar).
- **Very potent corticosteroid vs placebo:** The studies (Franz 2000, Olsen 1991, Jarratt 2004 and Sofen 2011) for scalp very potent corticosteroid vs. placebo ranged from two to four weeks duration, too short a timeframe to detect skin atrophy. As with potent steroid, foam formulations were more effective than lotion formulations; however the difference was not statistically significant for very potent corticosteroids. One study (Poulin 2010) looked at maintenance of response using very potent steroid vs placebo for up to 6 months but was noted to be of very low quality because once daily clobetasol propionate was permitted for up to 4 weeks if relapse occurred in clobetasol or vehicle group. During the whole study, clobetasol propionate was applied for 79.3 days in the clobetasol propionate group and 59.5 days in the vehicle group.
- **Potent corticosteroids vs vitamin D or vitamin D analogue:** There was unexplained heterogeneity between the studies (Jemec 2008, van der Kerkhof 2009 and Klaber 2004) for the efficacy outcomes, but betamethasone dipropionate was clinically beneficial compared to vitamin D or vitamin D analogue treatment.
- **Very potent steroids compared with other active treatments:** One study (Reygagne) compared very potent corticosteroid with vitamin D or vitamin D analogue treatment. The skin atrophy treatment effect was unclear because some atrophy was present at baseline. The GDG noted that there were no direct data comparing very potent steroids with other active treatments. However, from the network meta-analysis twice daily very potent corticosteroids were likely to be the most effective treatment. However, once daily potent corticosteroid or combined potent steroid and vitamin D analogue may be more effective than once daily very potent corticosteroid.
- **Combined product containing vitamin D analogue and potent steroid (calcipotriol monohydrate and betamethasone dipropionate) vs. vitamin D or vitamin D analogue alone:** There was heterogeneity between the 3 studies (Kragballe2009, Jemec 2008 and van de Kerkhof 2009) for the outcome of patient's assessment of scalp clearance comparing a product containing calcipotriol monohydrate and betamethasone dipropionate vs. vitamin D or vitamin D analogue alone. This may have been because Kragballe 2009 used a gel formulation of the combined preparation and a solution of vitamin D analogue, so the combination formulation may have been more effective than the vitamin D analogue comparator formulation. All 3 studies suggest that a

	combined product is clinically beneficial in terms of achieving clearance or near clearance compared with vitamin D or vitamin D analogue treatment alone. • **Coal tar:** The GDG commented that the 4-8 week follow-up in the studies (Griffiths 2006A and McKinnon 2000) assessing coal tar to treat scalp psoriasis was too short term to be able to draw any conclusions about the time to maximum effect. It is known from the trunk and limb data that coal tar takes a long time to act. Relapse rate is very low so coal tar probably does have a role in some patients. • In relation to different formulations, the GDG agreed that blinding was difficult especially with regard to tar and dithranol. • The MacKinnon study was not felt to reflect clinical practice as coal tar shampoos are usually used as an adjunct rather than monotherapy. **Scalp psoriasis in children** • The GDG commented on the lack of evidence for the treatment of children with psoriasis at difficult to treat sites; although two studies (Jarratt and Reygagne) included ages ≥12 the mean age in both was over 45 years. • The GDG agreed that the recommendations for adults could be extrapolated to children and young people **Face and flexural (including genital) psoriasis** Overall there are little data for psoriasis at the face and flexural sites, and no data for corticosteroids at these sites. Use of mild to moderate corticosteroids for face and flexural disease is accepted as standard practice and the lack of trial data of sufficient quality to be included in the review is disappointing but may reflect the historical usage. Therefore, based on clinical experience, the GDG agreed to make a recommendation for their use. Regarding the graphical data for time-to-maximum effect with tacrolimus the findings of the Lebwohl and Liao studies for improvement are conflicting. The Lebwohl study found that the number or people improving after 29 days treatment with tacrolimus was minimal. The Liao study found though that patients with clear / almost clear psoriasis increased by 20% between four and six weeks of treatment. The GDG noted that in the Lebwohl study 0.1% tacrolimus was used compared with 0.3% tacrolimus in the Liao study. Therefore, the differences were thought to be explained by the lower strength formulation taking longer to act.
Other considerations	The GDG noted there were no studies that addressed maintenance. As with trunk and limbs, an as-needed approach to use of topicals was appropriate. The point at which treatment should be reinstituted is based on patient need. Return of scale was felt to be significant by patient members of the group. **Scalp psoriasis** • It is difficult to assess skin atrophy on the scalp. • Use of corticosteroid on the scalp can be associated with

inadvertent application to the face with consequent risk of skin atrophy, facial acne. Therefore careful application is important.

- A post hoc subgroup analysis based on ethnicity (type V and VI skin) for the outcome of investigator's assessment of clear/nearly in the Tyring 2010 study found no significant difference between the subgroups when comparing the combined product containing calcipotriol monohydrate and betamethasone dipropionate scalp formulation (gel) vs. placebo. However, post-hoc analyses are intrinsically at high risk of bias and the GDG noted that the severity of psoriasis can be underestimated in people with type V and VI skin.
- Patient preference is an important factor in choosing a formulation to treat scalp psoriasis. The difference in cost of the formulations is small.
- The majority of the data on withdrawals (except withdrawals due to lack of efficacy for the placebo comparisons) and skin atrophy across all comparisons showed low event rates that gave very imprecise relative estimates, but in absolute terms demonstrated precise evidence of no clinically relevant difference between the interventions because the numbers involved were so low. Even in cases where there was a statistically significant difference in the interventions, such as withdrawals due to adverse events in the comparison of potent corticosteroids and placebo, in absolute terms there was no clinically significant difference between the interventions. The limitations to the studies in relation to steroid atrophy discussed in the trunk and limbs section also apply to high impact and difficult to treat and high impact sites (see 7.4.4 for trunk and limbs).
- The GDG felt that offering very potent corticosteroids first line would not be appropriate for scalp psoriasis. The GDG were mindful that the treatment is for long term use and relapse rates are higher with very potent steroids. Even use of potent steroid for scalp psoriasis in primary care would be a change in clinical practice. The GDG also noted that the majority of the evidence was from people with scalp psoriasis.
- From GDG experience, removing scale on the scalp before applying active treatment improves the efficacy of active treatment.

Face and flexures (including genitals)

- Calcineurin inhibitors are not prescribed for psoriasis in primary care as they are not licensed to treat psoriasis; however they are licensed and widely used in eczema.
- The GDG felt that intermittent short-term use of mild or moderately potent corticosteroids could be recommended in primary care but only for short-term use; use of topical calcineurin inhibitors should be on specialist advice given that these agents are unlicensed.
- The evidence suggested that for all interventions some level of response should be achieved by 4 weeks in those who are likely to gain benefit; therefore, the GDG agreed that it would be appropriate to review at 4 weeks to assess response to treatment. Additionally, for calcineurin inhibitors, the maximum response appears to be reached by 4 weeks so this was recommended as the treatment

	duration for this intervention. • The GDG debated the definition of relapse. Return of scale was felt to be significant by patient members of the group.

1

9 Phototherapy

The term phototherapy literally means the use of light, particularly ultraviolet (UV) light, to treat medical conditions. UVB and photochemotherapy (PUVA) are established treatments for psoriasis that are used for those patients in whom topical therapy has failed either to produce a satisfactory outcome or simply that their disease is too extensive for topical use to be practical. Generally, the phototherapies are employed for a significant proportion of moderate to severely affected individuals prior to systemic therapies for both plaque and guttate psoriasis. Phototherapy is also used to treat localised areas of psoriasis such as palmoplantar pustulosis.

Since 1990, broadband UVB (BBUVB) has gradually been replaced by a new fluorescent lamp, narrowband UVB (NBUVB). This light source omits the shorter and longer less therapeutically effective wavelengths. PUVA, following introduction in the early 1970's, quickly became an established treatment for generalised psoriasis.

UVB or PUVA is commonly given twice or three times weekly in courses which last several weeks and total between 15-30 treatments. Therapy is usually administered within hospital and involves significant time and travel commitments for patients. Maintenance therapy (e.g., treatments given weekly for long periods of time) is used in some centres, but is generally avoided to minimise adverse effects. Repeat courses, sometimes several in a year, are used in a minority of cases. Phototherapy is associated with both short term adverse effects, particularly risk of burning, and also in the long term, skin cancer.

As with other forms of therapy, the choice of treatment to employ depends on patient presentation and knowledge of previous treatment effectiveness and adverse effects. The lack of controlled studies relates to a relative lack of commercial, regulatory and grant funding interest. As phototherapy is not classified as a drug and therefore does not have the same vigorous study pre marketing requirements for clinical use.

Phototherapy is resource intensive to deliver in terms of personnel and equipment and a major commitment for patients. There is heterogeneity across England and Wales in terms of provision of the different types of phototherapy[14] and no explicit guidance available on use. The GDG were interested to review the evidence on the efficacy, and comparative efficacy, of all forms of phototherapy with particular focus on clearance rates and duration of remission, and adverse effects. Skin cancer risk associated with phototherapy is clearly a concern and was addressed separately in section 9.7.

The GDG agreed to ask the following question: in people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of broadband UVB, narrow band UVB and PUVA?

9.1 Methodological introduction

A literature search was conducted for RCTs or systematic reviews that compared the efficacy and safety of broadband UVB (BBUVB), narrowband UVB (NBUVB) and psoralen plus UVA (PUVA) with each other or with placebo/no treatment in people with psoriasis. Comparisons of treatment frequencies and of home- and hospital-based delivery of phototherapy were also considered. However, PUVA was restricted to oral or bath administered psoralen, except for palmoplantar pustulosis (PPP) for which cream psoralen administration was also included. No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The outcomes considered were:

- PASI75
- PASI50
- Change in PASI (mean improvement) or final PASI as a surrogate outcome
- Clear or nearly clear (minimal residual activity[MRA]/PASI>90/0 or 1 on PGA)
- Improved (for PPP population only)
- Time-to-relapse (loss of PASI50)
- Time-to-remission/max response
- Change in DLQI
- Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved)
- Cataracts
- Severe adverse events
- Withdrawal due to toxicity

Twenty three RCTs were found that addressed the question and were included in the review.

These studies differed in terms of their design and outcomes:

- 10 used within-patient randomisation[247-256]
- 13 used between-patient randomisation[257-269]
- 2 studies included children (12-16 years) and adults but did not stratify the results by age [264,268] and there were no studies assessing phototherapy in an exclusively paediatric population.
- 1 study used a modified PASI excluding assessment of the head [253]
- 1 study used a modified PASI excluding assessment of the palms, soles and head [251]
- 2 papers reported on the same study [266,267]
- Treatment frequency varied and is noted in the evidence statements. The standard frequencies in current practice are three-times weekly for BBUVB and NBUVB, and twice weekly for PUVA.

It was recognised that data from within-patient trials should be adjusted for the correlation coefficient relating to the comparison of paired data. However, none of the included studies reported this statistic and few reported sufficient detail for it to be calculated. There were two studies that presented data allowing for correction of the variance for the within patient correlation; one for the outcome of mean PASI[251], one for all reported outcomes except burn[250].

The studies also differed in terms of the characteristics of the included participants and whether the results were stratified according to skin type[270] (see Table 77).

Table 77: Baseline characteristics of included studies

Reference ID	Skin types	Results stratified by skin type	Disease types	Disease severity
AKMAN2008	Unclear	-	Unclear	No criteria, but mean baseline PASI = 10.65
CAMERON2002	I-III	N	Chronic plaque	Unclear
CHAUHAN2011	IV-V	N	Chronic plaque	BSA >20%
DAWE1998	I-III	N	Chronic plaque	Unclear
DAWE2003	I-III	N	Chronic plaque	Unclear
DAYAL2010	IV-V	N	Chronic plaque	BSA rule of nines ≥25%
ELMOFTY2008	III-IV	N	Chronic plaque	BSA 30-70%

Reference ID	Skin types	Results stratified by skin type	Disease types	Disease severity
GORDON1999	I-IV	N	Chronic plaque	Moderate-to-severe
HALLAJI2010	II-IV	N	Chronic plaque	BSA >10%
KIRKE2007	I-IV	Y	Plaque	No criteria, but mean baseline PASI = 6.8
KOEK2006	Unclear	-	Plaque or guttate psoriasis	Mild to severe; mean baseline PASI 9.15
KOEK2009	Unclear	-	Plaque or guttate psoriasis	Mild to severe; mean baseline PASI 9.15
LARKO1989	Unclear	-	Unclear	Baseline BSA 57%
MARKHAM2003	I-III	N	Chronic plaque	BSA rule of nines ≥8%
MURRAY1980	Unclear	-	Palmoplantar pustulosis	Unclear
PICOT1992	Unclear	-	Plaque and guttate	Widespread
ROSEN1987	Unclear	-	Palmoplantar pustulosis	Unclear
SERWIN2007	II-III	N	Early onset (before 40 years of age) plaque-type	No criteria, but mean baseline PASI = 40.8
SEZER2007	Unclear	-	Palmoplantar pustulosis	Unclear
SNELLMAN2004	II-IV	N	Chronic mostly plaque type	Mild-to-severe
STORBECK1993	I-IV	N	Plaque, guttate and erythrodermic	Widespread
VALBUENA2007	I-IV	Y	Plaque psoriasis	BSA ≥20% Mean PASI 31.85
YONES2006	I-VI	Y	Chronic plaque psoriasis	Moderate-to-severe disease (PASI >7; BSA rule of nines[(a)] ≥8%)

(a) Rule of nines: Each of the following body areas are weighted as 9% of the total: head, upper back, chest, right arm, left arm, lower back, abdomen, left upper leg, right upper leg, left lower leg, right lower leg.

The studies also differed in terms of the treatment frequency used for phototherapy, with some being sub-optimal. The usual frequencies are three-times weekly for BBUVB and NBUVB, and twice weekly for PUVA.

Where possible, the evidence was analysed by meta-analysis and GRADE, and these results are presented in a GRADE profile. Where studies reported data that could not be analysed by meta-analysis or GRADE, a narrative summary is provided below the GRADE profiles.

For meta-analysis the figures were based on an available case analysis rather than intention-to-treat analysis to avoid making assumptions about the participants for whom outcome data were unavailable. If there was a high drop-out rate for a study then a sensitivity analysis was performed to determine whether the effect was changed by using an intention-to-treat analysis, for the study with the high drop-out rate (other studies included in the same analysis remained as per protocol figures). This was found not to be the case on any occasion, as can be seen in the forest plots.

Data from within-patient trials should be adjusted for the correlation coefficient relating to the comparison of paired data. However, none of the included studies reported this statistic and few

reported sufficient detail for it to be calculated. There were two studies that presented data allowing for correction of the variance for the within patient correlation; one for the outcome of mean PASI[251], one for all reported outcomes except burn[250]. Where possible the within- and between-patient data were pooled even when this correction could not be made. This may result in underweighting of the within-patient studies; however this is a conservative estimate. Sensitivity analyses were undertaken to investigate whether the effect size varied consistently for within- and between-patient studies, there was no evidence of this. However it was often not possible to say if consistent differences were present as there was only one within patient study for a given comparison.

9.1.12 Narrowband vs broadband UVB

Table 78: Evidence profile comparing broadband vs narrowband UVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NBUVB	Selective BBUVB	Relative (95% CI)	Absolute	
Clear at end of treatment (follow-up to clear or no further improvement)											
1 Kirke 2007	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[a]	serious[b]	none	28/44 (63.6%)	20/41 (48.8%)	RR 1.30 (0.89 to 1.92)	146 more per 1000 (from 54 fewer to 449 more)	ÅÅÅO MODERATE
Clear at 3 months post-treatment (follow-up 3 months)											
1 Kirke 2007	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[a]	serious[b]	none	4/25 (16%)	8/18 (44.4%)	RR 0.36 (0.13 to 1.01)	284 fewer per 1000 (from 387 fewer to 4 more)	ÅÅÅO MODERATE
Clear at 6 months post-treatment (follow-up 6 months)											
1 Kirke 2007	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness[a]	very serious[d]	none	1/19 (5.3%)	0/13 (0%)	RR 2.1 (0.09 to 47.89)	500 more per 1000 (from 100 fewer to 200 more)	ÅOOO VERY LOW
Withdrawal due to toxicity (follow-up to clear or no further improvement)											
1 Kirke 2007	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[a]	very serious[d]	none	3/47 (6.4%)	1/42 (2.4%)	RR 2.68 (0.29 to 24.8)	40 more per 1000 (from 17 fewer to 567 more)	ÅÅOO LOW
Mean change in PASI (follow-up 10 weeks; better indicated by higher values)											
1 Picot 1992	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	serious[f]	none	15	15	Mean change in PASI 78.5% and 73.9% for NBUVB and BBUVB		ÅOOO VERY LOW
Improvement in PASI (follow-up 5-15 irradiations; better indicated by lower values)											
1 Storbeck 1993	randomised trials	very serious[g]	no serious inconsistency	no serious indirectness	serious[h]	none	10	10	Change in PASI: 50.23% with NBUVB; 36.28% with BBUVB (difference = 13.95%)		ÅOOO VERY LOW
Improvement in severity scores (follow-up 8 weeks; better indicated by lower values)											
1 Larko 1989	randomised trials	very serious	no serious inconsistency	serious[i]	serious	none	29	29	Change in severity score: 7.64 points with NBUVB; 6.68 points with BBUVB		ÅOOO VERY LOW

(a) Used selective BBUVB (UV6: little emission <290 nm)

(b) Confidence interval ranges from clinically important effect to no effect
(c) High level of missing data (32% in NBUVB and 35% in BBUVB groups)
(d) Confidence interval crosses the boundary for clinical significance in favour of both treatment, as well as line of no effect
(e) Unclear if allocation concealment performed and high drop-out rate (23.8%)
(f) No SD available
(g) Unclear allocation concealment and blinding
(h) No numerical data available
(i) Surrogate outcome for change in PASI

9.1.211 Evidence statements

In people with psoriasis there was no statistically significant difference between 3-times weekly selective BBUVB and 3-times weekly NBUVB for:

- Clear at the end of treatment [1 between-patient study; 85 participants; moderate quality evidence][257].
- Remaining clear at 3 months post treatment [1 between-patient study; 43 participants; moderate quality evidence][257].
- Remaining clear at 6 months post treatment [1 between-patient study; 32 participants; very low quality evidence][257].
- Withdrawal due to toxicity [1 between-patient study; 89 participants; low quality evidence][257].

Evidence statements for individual studies where no statistical analysis could be performed comparing 3-5-times weekly BBUVB and 3-5-times weekly NBUVB:

- One within-patient study found that both sides improved at 8 weeks although the improvement was slightly greater on the NBUVB-treated side [1 study; 29 participants (58 randomised units); very low quality evidence][248]. This study was randomised by order of exposure and not for which side of the body received which treatment.
- Two within-patient studies found that NBUVB was more effective than BBUVB
  - 1 study found that 3-5-times weekly NBUVB resulted in greater improvement in PASI than 3-5-times weekly BBUVB after 5-15 treatments [1 study; 10 participants (20 randomised units); very low quality evidence][249].
  - 1 study found that the average reductions in PASI at 10 weeks were 78.5% and 73.9% for NBUVB and BBUVB (both 3-times weekly), respectively, which was a statistically significant difference [1 study; 15 participants (30 randomised units); very low quality evidence][247]. Note that this study did not use equi-erythemogenic dosing.

9.1.3 Narrowband UVB vs PUVA

9.1.3.1 Oral PUVA (between patient randomisation)

Table 79: Evidence profile comparing narrowband UVB and oral PUVA

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NBUVB	Oral PUVA	Relative (95% CI)	Absolute	
Clear/nearly clear on PGA (within max number of Tx) - All skin types (follow-up up to 30-40 treatments)											
2 Gordon 1999 Yones 2006	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	55/85 (64.7%)	75/82 (91.5%)	RR 0.71 (0.6 to 0.84)	265 fewer per 1000 (from 146 fewer to 366 fewer)	⊕⊕OO LOW
Mean time to clearance (days) (follow-up 3 months; Better indicated by lower values)											
1 Dayal 2010	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 16.4 higher (7.31 to 25.49 higher)	⊕⊕⊕O MODERATE
Mean time to PASI75 (weeks) (follow-up 4 months; Better indicated by lower values)											
1 Chauhan , 2011	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	21	22	-	MD 0 higher (2.03 lower to 2.03 higher)	⊕OOO VERY LOW
Median time to clear (follow-up: treated to clearance; Better indicated by lower values)											
1 Markham 2003	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	serious[f]	none	21	24	PUVA: 66 days (95% CI: 52.0-92.0) NBUVB: 67 days (95% CI: 47.9-81.7) p-value: 0.46		⊕⊕OO LOW

PASI75 (follow-up 3-4 months or 20 treatments)											
3 Serwin, 2007 Dayal, 2010 Chauhan, 2011	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/76 (89.5%)	67/77 (87%)	RR 1.03 (0.92 to 1.15)	26 more per 1000 (from 70 fewer to 131 more)	⊕⊕⊕O MODERATE
Median change in PASI (follow-up 10 weeks; Better indicated by higher values)											
1 Yones, 2006	randomised trials	serious[h]	no serious inconsistency	no serious indirectness	serious[f]	none	34	37	-	PUVA: -6.8 NBUVB: -3.9	⊕⊕OO LOW
Mean change in PASI (2 months) (Better indicated by higher values)											
1 Akman, 2008	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	serious[j]	none	20	18	-	PUVA: -12.4 NBUVB: -6.6	⊕OOO VERY LOW
Final PASI (surrogate for change in PASI) – three-times weekly UV (follow-up 20 treatments; Better indicated by lower values)											
1 Serwin, 2007	randomised trials	serious[k]	no serious inconsistency	serious[l]	serious[l]	Note: change scores PUVA: -11.67 NBUVB: -11.90	25	25	-	MD 1.08 lower (2.13 to 0.03 lower)	⊕OOO VERY LOW
Final PASI (surrogate for change in PASI) – twice weekly UV (follow-up 3 months; Better indicated by lower values)											
1 Dayal, 2010	randomised trials	serious[c]	no serious inconsistency	serious[l]	serious[m]	Note: change scores PUVA: -20.21 NBUVB: -15.22	30	30	-	MD 0.21 higher (0.3 lower to 0.72 higher)	⊕OOO VERY LOW
Relapse rate (follow-up 6-12 months post-treatment)											
4 Chauhan, 2011 Gordon,	randomised trials	no serious imprecision[n]	no serious inconsistency	serious[l]	no serious imprecision	none	67/93 (72%)	47/103 (45.6%)	RR 1.55 (1.22 to 1.97)	251 more per 1000 (from 100 more to 443 more)	⊕⊕⊕O MODERATE

1999 Yones, 2006 Markham 2003											
Median time to relapse (follow-up 12 months; Better indicated by higher values)											
1 Markham2003	randomised trials	serious[o]	no serious inconsistency	no serious indirectness	serious[f]	none	23	34	PUVA: 231 (162.7-365.0) days NBUVB: 288.5 (170.6-365.0) days Mann-Whitney p-value: 0.40		⊕⊕OO LOW
Median time to relapse (follow-up 12 months; Better indicated by higher values)											
1 Yones, 2006	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	serious[f]	none	21	24	PUVA: 8 months NBUVB: 4 months Logrank p-value: 0.03[p]		⊕⊕OO LOW
Withdrawal due to toxicity (follow-up to 30-40 treatments)											
2 Gordon 2003 Yones, 2006	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	3/79 (3.8%)	4/85 (4.7%)	RR 0.88 (0.23 to 3.31)	6 fewer per 1000 (from 36 fewer to 109 more)	⊕OOO VERY LOW

(a) 1/2 studies had unclear allocation concealment (sequentially numbered list); 1/2 studies had a high drop-out rate (35%) in NBUVB arm
(b) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(c) Unclear if allocation concealment was performed
(d) No allocation concealment and unclear blinding
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatment, as well as line of no effect
(f) No range or SD available
(g) 2/3 unclear allocation concealment and 1/3 no allocation concealment; 2/3 unclear blinding
(h) Unclear if allocation concealment performed and high drop-out rate in NBUVB group (35%)
(i) Unclear study methodology
(j) No SD available
(k) Unclear if allocation concealment and blinding performed
(l) Surrogate outcome measure
(m) Confidence interval ranges from a clinically important effect to no effect
(n) No allocation concealment and unclear blinding; high drop-out rate
(o) Unclear allocation concealment (sequentially numbered list); high drop-out rate (35%) in NBUVB arm

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9.1.312 Evidence statements

In people with psoriasis two- or three-times weekly oral PUVA was statistically significantly better than two- or three-times weekly NBUVB for:

- Clear or nearly clear on PGA at the end of treatment (maximum 30-40 treatments) [2 between-patient studies; 167 participants; low quality evidence][258,263]
- Relapse rate for clearers after 6-12 months [4 between-patient studies; 196 participants; moderate quality evidence] [258,260,263,269]
- Mean time to clearance after a maximum follow-up of 3 months [1 between-patient study; 60 participants; moderate quality evidence] [259]

In people with psoriasis three-times weekly NBUVB was statistically significantly better than three-times weekly oral PUVA for:

- Final PASI score (*three-times weekly UV*) after a maximum of 20 treatments [1 between-patient study; 50 participants; very low quality evidence][261]

In people with psoriasis there was no statistically significant difference between two- or three-times weekly NBUVB and two- or three-times weekly PUVA for:

- PASI75 (*skin type II – III or IV – V*) at 3-4 months or after a maximum of 20 treatments [3 between-patient studies; 153 participants; moderate quality evidence] [259,261,269]
- Final PASI score (*twice-weekly UV*) at 3 months [1 between-patient study; 60 participants; very low quality evidence] [259]
- Mean time to PASI75 after a follow-up of 4 months [1 between-patient study; 43 participants; very low quality evidence][269]
- Withdrawal due to toxicity after a maximum 16-30 treatments [2 between-patient studies; 164 participants; very low quality evidence] [258,263]

Evidence statements for individual studies where no original analysis could be performed comparing narrowband UVB and PUVA:

- One study found that there was a longer time to relapse with twice weekly PUVA compared with twice weekly NBUVB after a maximum follow-up of 12 months [1 between-patient study; 57 participants; low quality evidence][258]
- One study found that there was no significant difference in time to relapse with twice weekly PUVA compared with three-times weekly NBUVB after a maximum follow-up of 12 months [1 between-patient study; 45 participants; low quality evidence][260]
- Two studies found that there was a greater mean or median change in PASI with two- or three-times weekly PUVA than two- or three-times weekly NBUVB at 8-10 weeks [2 between-patient studies; 109 participants; low to very low quality evidence][258,262]
- One study found that there was a no significant difference in median time to clearance between twice weekly PUVA and three-times weekly NBUVB [1 between-patient study; 45 participants; low quality evidence][260]

9.1.383 Subgroup analysis and heterogeneity

Data were available for different skin types based on the Fitzpatrick classification between studies and as a post-hoc subgroup analysis in one study.

- There was significant heterogeneity for the outcome of final PASI between two studies[259,261]. This could be explained by pre-defined subgroups based on skin type (II-III[261] and IV-V[259]). However, it was felt to be more likely that the heterogeneity was due to differences in treatment frequency

between the studies as skin type variation would have been accounted for in the calculation of the minimal erythrogenic dose. One study[261] using 3-times weekly administration (optimal for UVB but higher than usual for PUVA) and the other[259] twice-weekly administration (sub optimal for NBUVB but usual for PUVA) of both interventions. There was no significant heterogeneity between these two studies for the outcome of PASI75.

- One study[258] presented a post-hoc subgroup analysis for different skin types for the outcome of clear or nearly clear on PGA. The samples sizes in the type V-VI subgroup were very small (see Figure 12 in Appendix C.2.2) making it difficult to draw any conclusions about the relative difference in effectiveness of NBUVB and PUVA. There was a high, but not statistically significant, degree of difference between the subgroups (I^2 = 47.6%) and the proportion responding to either kind of light treatment was markedly lower in the skin type V-VI subgroup (23.5%) than the I-IV subgroup (74.6%).

9.1.3.14 Bath PUVA

Table 80: Evidence profile comparing narrowband UVB and bath PUVA

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	NBUVB	Bath PUVA	Relative (95% CI)	Absolute	
Time-to-remission (clearance or minimal residual activity) (follow-up maximum 30 treatments)											
1 Dawe 2003	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	Median PUVA: 86 days NBUVB: 61 days	28	28	HR 3.53 (1.99 to 6.26)	398 more per 1000 (from 247 more to 456 more)[b]	⊕⊕⊕O MODERATE
Mean change in PASI (Better indicated by higher values) (follow-up 10 weeks)											
1 Snellman, 2004	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[c]	none	14	14	-	MD 2.71 higher (1.49 higher to 3.93 higher)	⊕⊕⊕O MODERATE
Mean days to relapse (follow-up 6.5 months; Better indicated by higher values)											
1 Dawe 2003	randomised trials	serious1	no serious inconsistency	no serious indirectness	serious[d]	none	21	15	-	MD 39.27 higher (8.71 higher to 69.83 higher)	⊕⊕OO LOW
Withdrawal due to toxicity (follow-up 10 weeks)											
1 Snellman, 2004	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[e]	none	0/15 (0%)	1/15 (6.7%)	RR 0.33 (0.01 to 7.58)	45 fewer per 1000 (from 66 fewer to 439 more)	⊕⊕OO LOW
Burn (follow-up maximum 30 treatments)											
1 Dawe	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	4/28 (14.3	4/28 (14.3	RR 1 (0.28 to 3.61)	0 fewer per 1000 (from 103 fewer to	⊕OOO VERY LOW

Quality assessment							Summary of findings				
2003							%)	%)		373 more)	

(a) High drop-out rate (35.7%)
(b) Absolute calculation based on control group risk at study end-point
(c) Confidence interval ranges from clinically important effect to no effect
(d) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

9.1.315 Evidence statements

In people with psoriasis there was three-times weekly NBUVB was statistically significantly better than twice weekly bath PUVA for:

- Time-to-remission (clearance or minimal residual activity) after a maximum of 30 treatments [1 within-patient study; 28 participants (56 randomised units); moderate quality evidence][250]
- Mean change in PASI at 10 weeks [1 within-patient study; 14 participants (28 randomised units); moderate quality evidence][251]
- Mean days to relapse after a maximum follow-up of 6.5 months [1 within-patient study; 21 participants (36 randomised units); low quality evidence][250]

In people with psoriasis there was no statistically significant difference between three-times weekly NBUVB and two- or three-times weekly bath PUVA for:

- Withdrawal due to toxicity at 10 weeks [1 within-patient study; 15 (30 randomised units) participants; low quality evidence][251]
- Burn after a maximum of 30 treatments [1 within-patient study; 28 participants (56 randomised units); very low quality evidence] [250]

9.1.4 Different NBUVB treatment frequencies

9.1.4.1 NBUVB five-times vs three-times weekly

Table 81: Evidence profile comparing narrowband UVB five times vs three times weekly

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NBUVB 5x	NBUVB 3x	Relative (95% CI)	Absolute	
Clearance (follow-up until clearance (range: 4.7-23 weeks) or a maximum of 30 treatments)											
2 Dawe, 1998 Hallaji, 2010	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision[b]	none	31/41 (75.6%)	34/42 (81%)	RR 0.93 (0.74 to 1.17)	57 fewer per 1000 (from 210 fewer to 138 more)	⊕⊕⊕O MODERATE
Mean time to clearance (follow-up to clearance (range: 4.7-23 weeks); better indicated by lower values)											
1 Hallaji 2010	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	15	18	-	3-times: 13.7 (11.4-15.9) weeks 5-times: 7.9 (6.7-9.0) weeks	⊕⊕OO LOW
Median time to clearance (better indicated by lower values) (follow-up to a maximum of 30 treatments)											
1 Dawe 1998	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	median 5 higher (2 to 11 higher) 3-times: 40 (23-63) days 5-times: 35 (19-43) days P = 0.007; 95% CI: 2-11	⊕⊕⊕O MODERATE
Median time to relapse (better indicated by lower values) (follow-up 12 months)											
1 Dawe	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	19	19	-	3-times:165 days 5-times:174 days	⊕OOO VERY LOW

1998										p = 0.73 from log-rank test[f]	
Withdrawal due to toxicity (follow-up to clearance (range: 4.7-23 weeks))											
1 Hallaji 2010	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/19 (0%)	0/19 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Burn (follow-up to a maximum of 30 treatments)											
1 Dawe 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/33 (0%)	0/32 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE

(a) Unclear if allocation concealment was performed and high drop-out rate (28% for 3-times and 33% for 5-times weekly)
(b) Precise according to GDG discussion (confidence interval lies completely within effect estimates that indicate no clinically important benefit/harm)
(c) No SD reported
(d) Unclear if allocation concealment was performed and not stated if plaques were symmetrical
(e) No measure of variance and read from graph
(f) Event rate not available so hazard ratio could not be calculated

9.1.412 Evidence statements

In people with psoriasis there was no statistically significant difference between 3- and 5-times weekly NBUVB for:

- Clearance at 23 weeks or after a maximum of 30 treatments [2 studies (one between-patient and one within-patient); 64 participants (83 randomised units); moderate quality evidence][252,264]

In people with psoriasis there were no events with either 3- or 5-times weekly NBUVB for:

- Burn after a maximum of 30 treatments [1 between-patient study; 65 participants; moderate quality evidence] [264]
- Withdrawal due to toxicity at 23 weeks [1 within-patient study; 19 participants (38 randomised units); moderate quality evidence] [252]

Evidence statements for individual studies where no original analysis could be performed comparing narrowband UVB 3- vs 5-times weekly:

- 2 studies showed that 5-times weekly NBUVB resulted in a shorter time to clearance that 3-times weekly NBUVB after a maximum of 23 weeks [2 studies (one between-patient and one within patient); 52 participants (71 randomised units); low to moderate quality evidence][252,264]
- 1 study showed that there was no significant difference in time to relapse with 3- and 5-times weekly NBUVB after a maximum follow-up of 12 months [1 within-patient study; 19 participants (38 randomised units); very low quality evidence][252]

9.1.413 Narrowband UVB two times vs three times weekly

Table 82: Evidence profile comparing narrowband UVB two times vs three times weekly

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	NBUVB 2x	NBUVB 3x	Relative (95% CI)	Absolute	
Clearance (follow-up until clear or minimal residual activity maintained for at least 4 treatment visits)											
1 Cameron 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/44 (90.0%)	44/48 (91.7%)	RR 0.99 (0.87 to 1.13)	9 fewer per 1000 (from 119 fewer to 119 more)	⊕⊕⊕O MODERATE
Mean days to clearance; better indicated by lower values (follow-up until clear or minimal residual activity maintained for at least 4 treatment visits)											
1 Cameron 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	58	55	-	2-times: 88 (48-150) days 3-times: 58 (32-112) days P <0.0001	⊕⊕OO LOW
Median time to relapse; better indicated by higher values (follow-up 12 months post-treatment)											
1 Cameron 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	58	55	-	Relapse defined as requiring topicals other than emollients: 2-times: 4.7 months 3-times: 3.8 months P =0.53 from log rank test[d] Relapse defined as requiring phototherapy or other second line: 2-times: 21.3 months 3-times: 17.0 months P =0.73 from log rank	⊕OOO VERY LOW

Quality assessment							Summary of findings				
										test[d]	
Withdrawal due to toxicity (follow-up until clear or minimal residual activity for at least 4 treatment visits)											
1 Cameron 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	2/42 (4.8%)	1/45 (2.2%)	RR 2.14 (0.2 to 22.77)	25 more per 1000 (from 18 fewer to 484 more)	⊕OOO VERY LOW
Burn (follow-up until clear or minimal residual activity for at least 4 treatment visits)											
1 Cameron 2002	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	10/58 (17.2%)	12/55 (21.8%)	RR 0.79 (0.37 to 1.68)	46 fewer per 1000 (from 137 fewer to 148 more)	⊕OOO VERY LOW

(a) High drop-out rate (25.7%)
(b) No SD given
(c) No measure of variance and read from graph
(d) Event rate not available so hazard ratio could not be calculated
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

9.1.414 Evidence statements

In people with psoriasis there was no statistically significant difference between 2- and 3-times weekly NBUVB for:

- Clearance [1 between-patient study; 92 participants; moderate quality evidence][265]
- Withdrawal due to toxicity [1 between-patient study; 87 participants; very low quality evidence][265]
- Severe UV erythema (burn) [1 between-patient study; 113 participants; very low quality evidence][265]

Evidence statements for individual studies where no original analysis could be performed comparing narrowband UVB 2- vs 3-times weekly:

- 1 study showed that 3-times weekly NBUVB resulted in a shorter time to clearance that 2-times weekly [1 study; 113 participants; low quality evidence][265]
- 1 study showed that 2-times weekly NBUVB resulted in a longer time to relapse that 3-times weekly after a maximum follow-up of 12 months post-treatment [1 study; 113 participants; low quality evidence][265]

9.1.415 Different oral PUVA treatment frequencies (3 vs 2 times weekly)

Table 83: Evidence profile comparing different oral PUVA treatment frequencies (3 vs 2 times weekly)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PUVA 3x	PUVA 2x	Relative (95% CI)	Absolute	
Clear/nearly clear on IAGI (follow-up 12 weeks)											
1 El-Mofty 2008	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [b]	none	4/9 (44.4%)	9/10 (90%)	RR 0.49 (0.23 to 1.05)	459 fewer per 1000 (from 693 fewer to 45 more)	⊕⊕OO LOW
% Change in PASI (follow-up 12 weeks; Better indicated by higher values)											
1 El-Mofty 2008	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	serious [b]	none	9	10	-	MD 15.43 lower (37.66 lower to 6.8 higher)	⊕⊕OO LOW
Median change in PASI (follow-up up to 25 treatments; Better indicated by higher values)											
1 Valbuena 2007	randomised trials	serious [c]	no serious inconsistency	no serious indirectness	serious [d]	none	28	28	-	See Table 84	⊕⊕OO LOW
Burn (follow-up upto 25 treatments)											
1 Valbuena 2007	randomised trials	serious [c]	no serious inconsistency	no serious indirectness	very serious [e]	none	1/23 (4.3%)	0/23 (0%)	RR 3 (0.13 to 70.02)	40 more per 1000 (from 70 fewer to 160 more)	⊕OOO VERY LOW

(a) Unclear if allocation concealment performed and not stated if plaques were symmetrical
(b) Confidence interval ranges from clinically important effect to no effect
(c) Unclear if allocation concealment performed and not stated if plaques were symmetrical
(d) No range or SD given
(e) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect

9.1.416 Evidence statements

In people with psoriasis there was no statistically significant difference between 2- and 3-times weekly oral PUVA for:

- Clear/nearly clear on IAGI at 12 weeks [1 between-patient study; 19 participants; low quality evidence][268]
- Percentage change in PASI at 12 weeks [1 between-patient study; 19 participants; low quality evidence][268]
- Burn at a maximum of 25 treatments [1 within-patient study; 23 participants (46 randomised units); very low quality evidence][253]

9.1.417 Subgroup analysis and heterogeneity

Data were available for percentage change in PASI up to 25 treatments for different skin types based on the Fitzpatrick classification and for different psoriasis phenotypes (see Glossary).

Table 84: Summary of non-analysed data for PUVA 2 vs 3 times weekly

Study	Result					Treatment favoured	Grade rating
Valbuena		N	2-times a week	3-times a week	p-value	No difference for total group 2-times weekly better for skin types III-IV and the ostraceous subtype of psoriasis	LOW
	Skin type I	6	91.5 (89.9-97.1)	93.2 (91.8-94.0)	0.673		
	Skin type III-IV	17	93.1 (91-94.9)	95.5 (93.0-96.8)	0.079		
	Vulgaris	16	93.6 (92.6-96.4)	95.2 (79.1-99.2)	0.972		
	Ostraceous	7	90.5 (87.3-91.1)	94.0 (92.8-96.0)	0.043		
	Total group	*23*	*92.9 (89.9-96.1)*	*94.8 (91.8-96.8)*	*0.179*		

- 1 study showed that there was no significant difference for median change in PASI between oral PUVA 2- and 3-times weekly after a maximum of 25 treatments [1 within-patient study; 28 participants (56 randomised units); low quality evidence][253]
- Oral PUVA 2-times weekly resulted in a greater median decrease in PASI after a maximum of 25 treatments for skin types III-IV and for the ostraceous subtype of psoriasis (this is an infrequently used term to describe plaque-type psoriasis that is particularly hyperkeratotic, typically with relatively concave centres, similar in shape to oyster shells) [1 within-patient study; 28 participants (56 randomised units); very low quality evidence][253]

9.1.418 Oral PUVA vs no treatment for palmoplantar pustulosis

2 **Table 85: Evidence profile**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oral PUVA	No treatment	Relative (95% CI)	Absolute	
Clearance (follow-up 7.5-12 weeks)											
2 Murray 1980 Rosen 1987	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/34 (44.1%)	0/34 (0%)	RR 16 (2.23 to 114.89)	440 more per 1000 (from 270 more to 620 more)4	⊕⊕⊕O MODERATE
Improved (follow-up 7.5-12 weeks)											
2 Murray 1980 Rosen 1987	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/34 (94.1%)	17/34 (50%)	RR 1.86 (1.32 to 2.6)	430 more per 1000 (from 160 more to 800 more)	⊕⊕⊕O MODERATE
Withdrawal due to toxicity (follow-up 7.5-12 weeks)											
2 Murray 1980 Rosen 1987	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/35 (2.9%)	0/34 (0%)	RR 2.79 (0.12 to 62.48)	30 more per 1000 (from 60 fewer to 120 more)[d]	⊕OOO VERY LOW
Burn (follow-up 7.5-12 weeks)											
2 Murray 1980 Rosen 1987	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	5/34 (14.7%)	0/34 (0%)	RR 6 (0.77 to 46.79)	150 more per 1000 (from 10 fewer to 280 more) [d]	⊕⊕OO LOW

(a) 2/2 studies had unclear blinding of assessor (allocation concealment was also unclear but disease was bilaterally symmetrical)
(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(c) Confidence interval ranges from a clinically important effect to no effect
(d) Calculated from risk difference

9.1.419 Evidence statements

In people with palmoplantar pustulosis oral PUVA 3 or 4 times weekly for hand and foot palmoplantar pustulosis was statistically significantly better than no treatment for:

- Clearance at 7.5-12 weeks [2 within-patient studies; 34 participants (68 randomised units); moderate quality evidence][254,255]
- Improvement at 7.5-12 weeks [2 within-patient studies; 34 participants (68 randomised units); moderate quality evidence] [254,255]

In people with palmoplantar pustulosis there was no statistically significant difference between 3- or 4-times weekly oral hand and foot PUVA and no treatment for:

- Withdrawal due to toxicity at 7.5-12 weeks [2 within-patient studies; 35 participants (69 randomised units); very low quality evidence] [254,255]
- Burn at 7.5-12 weeks [2 within-patient studies; 34 participants (68 randomised units); low quality evidence] [254,255]

9.1.4.10 Cream PUVA vs narrowband UVB for hand and foot palmoplantar pustulosis

Table 86: Evidence profile

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	NBUVB	Cream PUVA	Relative (95% CI)	Absolute	
Clear/nearly clear on IAGI (follow-up 9 weeks)											
1 Sezer 2007	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/21 (42.9%)	20/21 (95.2%)	RR 0.45 (0.27 to 0.74)	524 fewer per 1000 (from 248 fewer to 695 fewer)	⊕⊕⊕O MODERATE
Withdrawal due to toxicity (follow-up 9 weeks)											
1 Sezer 2007	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/21 (0%)	1/22 (4.5%)	RR 0.35 (0.01 to 8.11)	30 fewer per 1000 (from 45 fewer to 323 more)	⊕OOO VERY LOW
Relapse (follow-up 10 weeks post treatment)											
1 Sezer 2007	randomised trials	serious[a]	no serious inconsistency	serious[c]	serious[d]	none	10/21 (47.6%)	4/21 (19%)	RR 2.5 (0.93 to 6.72)	286 more per 1000 (from 13 fewer to 1000 more)	⊕OOO VERY LOW

(a) Unclear if allocation concealment performed and not stated if disease was symmetrical
(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect
(c) Surrogate outcome for time-to-relapse
(d) Confidence interval ranges from a clinically important effect to no effect

9.1.4.11 Evidence statements

In people with palmoplantar pustulosis three-times cream hand and foot PUVA was statistically significantly better than NBUVB three-times weekly for:

- Clear or nearly clear at 9 weeks [1 within-patient study; 21 participants (42 randomised units); moderate quality evidence][256]

In people with palmoplantar pustulosis there was no statistically significant difference between cream hand and foot PUVA three-times weekly and NBUVB three-times weekly for:

- Withdrawal due to toxicity at 9 weeks [1 within-patient study; 22 participants (43 randomised units); very low quality evidence][256]
- Relapse 10 weeks after treatment [1 within-patient study; 21 participants (42 randomised units); very low quality evidence][256]

9.1.4.112 Home vs hospital NBUVB for psoriasis

2 **Table 87: Evidence profile**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Home	Hospital	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90) (follow-up mean 11.4 weeks for home and 14.1 weeks for hospital; maximum of 46 treatments)											
1 Koek, 2006; Koek, 2009	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	18/94 (19.1%)	16/91 (17.6%)	RR 1.09 (0.59 to 2)	16 more per 1000 (from 72 fewer to 176 more)	⊕⊕OO LOW
PASI 75 (follow-up mean 11.4 weeks for home and 14.1 weeks for hospital; maximum of 46 treatments)											
1 Koek, 2006; Koek, 2009	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	37/94 (39.4%)	35/91 (38.5%)	RR 1.02 (0.71 to 1.47)	8 more per 1000 (from 112 fewer to 181 more)	⊕⊕OO LOW
PASI 50 (follow-up mean 11.4 weeks for home and 14.1 weeks for hospital; maximum of 46 treatments)											
1 Koek, 2006; Koek, 2009	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/94 (68.1%)	61/91 (67%)	RR 1.02 (0.83 to 1.24)	13 more per 1000 (from 114 fewer to 161 more)	⊕⊕⊕⊕ HIGH
% with side effect per irradiation (follow-up mean 11.4 for home and 14.1 weeks for hospital; maximum of 46 treatments)											
1 Koek, 2006; Koek, 2009	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[b]	none	93	92	-	Home Hospital Difference (95%CI) Severe erythema 5.5 3.6 1.9 (−1.1 to 4.9) Blistering 0.3 0.6 −0.3 (−0.9 to 0.3) Burning sensation 7.1 10.0 −2.9 (−7.1 to 1.2)	⊕⊕OO LOW

1
2 *(a) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as line of no effect*
3 *(b) No numerical data provided for number of adverse events in each group*

4

9.1.4.13 Evidence statements

In people with psoriasis there was no statistically significant difference between 3- or 4-times weekly NBUVB home and 2- or 3-times weekly hospital NBUVB for:

- Clear/nearly clear (PASI90) after a maximum of 46 treatments [1 between-patient study; 185 participants; low quality evidence][266,267]
- PASI75 after a maximum of 46 treatments [1 between-patient study; 185 participants; low quality evidence] [266,267]
- PASI50 after a maximum of 46 treatments [1 between-patient study; 185 participants; high quality evidence] [266,267]

Evidence statements for outcomes where no original analysis could be performed comparing 3- or 4-times weekly NBUVB home and 2- or 3-times weekly hospital NBUVB for:

- There was no meaningful difference between the number of participants experiencing severe UV erythema, blistering or a burning sensation after a maximum of 46 treatments [1 between-patient study; 185 participants; low quality evidence] [266,267].

9.1.5 Economic evidence

An economic evaluation should ideally compare all relevant alternatives. No studies were identified comparing all three interventions of interest – broadband UVB, narrowband UVB and PUVA – in the treatment of patients with psoriasis.

One study[271] was included that compared narrowband UVB delivered in the home with narrowband UVB delivered in an outpatient unit. It is summarised in the economic evidence profile below (Table 88 and Table 89). One study[272] was included that compared PUVA with broadband UVB. It is summarised in the economic evidence profile below (Table 90 and Table 91). One study[273] was included that compared PUVA with narrowband UVB. It is summarised in the economic evidence profile below (Table 92 and Table 93). All of these studies are summarised in full in the study evidence tables in Appendix I.

One study[274] was excluded from this review, due to it not being applicable and having very serious limitations. Reasons for its exclusion are provided in Appendix G.

No relevant economic evaluations comparing broadband UVB with NBUVB were identified.

Table 88: Home NBUVB versus outpatient NBUVB – economic study characteristics

Study	Limitations	Applicability	Other comments
Koek (2010)[271]	Potentially serious limitations (a)	Partially applicable (b)	Trial-based economic evaluation conducted alongside the PLUTO study[266]

(a) One-year time horizon – sufficient for evaluation of phototherapy, but does not capture consequences of treatment failure; sensitivity analyses conducted but could not be considered due to the inclusion of direct and indirect non-medical costs.

(b) Costing perspective is Dutch society: some uncertainty about applicability of Dutch unit costs; EQ-5D measured at baseline and 3 months, but imputed EQ-5D for 12-month follow-up based on SAPASI score, gender and employment status.

Table 89: Home NBUVB versus outpatient NBUVB – economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Koek (2010) at completion of phototherapy	£182 (a)	0.0052 (b)	£34,967 per QALY	95% CI for incrmntl cost: £38 to £225 95% CI for incrmntl effect: -0.0244 to 0.0348 1000 bootstrapped replications (where direct and indirect non-medical costs were included) indicate that NBUVB delivered at home had a 56.9% probability of being cost-effective at £13,800 (€20,000) per QALY.
Koek (2010) at 12 months after phototherapy	£198 (a)	0.0267 (c)	£7,432 per QALY	95% CI for incrmntl cost: £35 to £362 95% CI for incrmntl effect: -0.024 to 0.078 1000 bootstrapped replications (where direct and indirect non-medical costs were included) indicate that NBUVB delivered at home had 76.3% and 79.2% probabilities of being cost-effective at £13,800 (€20,000) and £20,700 (€30,000) per QALY, respectively.

(a) Direct medical costs only; converted from 2003 Dutch Euros.
(b) QALYs measured directly from patients.
(a) QALYs imputed based on SAPASI score, gender and employment status

Koek (2010) indicates that in terms of quality of life gains, there is little difference between NBUVB delivered in the home and NBUVB delivered in an outpatient setting. However, there is a significant difference in direct medical costs. The utility scores reported at one year following treatment are not based on direct measurement, but are rather based on an algorithm informed by SAPASI score, gender and employment status. It is unclear whether this method under or over estimates true quality of life benefits.

Although direct and indirect non-medical costs could be separated from the base case results, they could not be removed from the results of the sensitivity analyses. It is uncertain what impact this has on the overall results, but it could be substantial. In the base case results, when non-medical costs were included, there were no statistically significant differences in total costs between treatments. But as shown above, when only medical costs are included, there is a significant difference. Given this, one could argue that the likelihood that home NBUVB is more cost-effective at a threshold of £20,000 is less than the 79.2% probability in the base case.

Table 90: PUVA versus broadband UVB – economic study characteristics

Study	Limitations	Applicability	Other comments
Marchetti (2005)[272]	Very serious limitations (a)	Partially applicable (a)	Decision analytic model; treatment effects estimated from Iest 1989[275] and Lauharanta 1981 for induction of remission and Koo 1999 for maintenance of remission.

(a) Treatment effect estimates based on an unadjusted indirect comparison from an unsystematic review of evidence; costs of treatment failures ignored; no sensitivity analyses reported.
(b) Some uncertainty about applicability of US clinical practice, estimates of resource use and unit costs; QALYs not used.

Table 91: PUVA versus broadband UVB – economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Marchetti (2005)	£210 (a)	10.3 more remission days	£20 per additional remission day	No sensitivity analysis reported

(a) Converted from 2003 US Dollars.

Marchetti (2005) used number of remission days as their primary outcome measure. If we assume that these 10.3 additional days of remission were associated with a 0.19 gain in utility (based on utility gain estimates for a PASI75 to PASI90 response from Woolacott and colleagues[276]), then it would translate to approximately 0.0054 QALYs. The incremental cost effectiveness ratio for PUVA compared to broadband UVB would then be £39,167 per QALY gained. However, it is important to recognise that the effect estimates used to determine the expected number of remission days are based on an unsystematic review of the available evidence and the authors do not justify their reasons for choosing particular data sources. The authors also did not explore the uncertainty in their results through sensitivity analysis.

Table 92: PUVA versus narrowband UVB – economic study characteristics

Study	Limitations	Applicability	Other comments
Pearce (2006)[273]	Very serious limitations (a)	Partly applicable (b)	Simple decision analytic model; treatment effects estimated as a weighted mean probability of PASI 75 response from Gordon 1999 and an unknown reference

(a) 12-week time horizon may be insufficient to evaluate effectiveness of interventions and capture consequences of treatment failures; treatment effects estimated from an unadjusted indirect comparison from a systematic review of RCT evidence; no sensitivity analyses reported; funded by Galderma Laboratories
(b) Some uncertainty about applicability of US clinical practice, estimates of resource use and unit costs; QALYs not used.

Table 93: PUVA versus Narrowband UVB – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Pearce (2006)	£810 (a)	12% more achieving PASI75 or total body clearance	£67 per additional 1% achieving PASI75 or total body clearance	A series of deterministic sensitivity analyses were performed, but effect on base case results could not be determined from the report.

(a) Converted from 2003 US Dollars

Pearce and colleagues (2006) used the proportion of participants achieving a PASI75 or total body clearance as their primary outcome measure. The 12-week time horizon of the analysis should be considered a significant limitation because it is not sufficiently long enough to capture the true effects of the interventions being evaluated, nor is it long enough to account for the costs and consequences of participants who do not achieve a PASI75 or total body clearance.

It is also worth noting that the analysis included non-biological systemic therapies – acitretin, ciclosporin, methotrexate – as comparators. Looking at the overall results, narrowband UVB was dominated by (more costly and less effective than) ciclosporin, and PUVA was more costly and more

effective than ciclosporin with an ICER of £934 per additional 1% achieving PASI75 or total body clearance.

9.1.531 Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Item	Cost	Notes
Phototherapy	£82	NHS Reference Costs 2009/10 for phototherapy (JC29Z) delivered in an outpatient setting
Photochemotherapy	£131	NHS Reference Costs 2009/10 for phototherapy (JC32Z) delivered in an outpatient setting

Source: NHS Reference Costs 2009/10[277]

9.1.572 Economic evidence statements

- No cost-effectiveness analyses were identified comparing all three interventions of interest – broadband UVB, narrowband UVB and PUVA – in the treatment of patients with psoriasis.
- One partially applicable study with potentially serious limitations found that in a population with psoriasis eligible for treatment with phototherapy, narrowband UVB delivered in the home was more costly and more effective than narrowband UVB delivered in an outpatient setting, with an ICER of £34,967 during treatment and £7,432 in the year following treatment. There is considerable uncertainty as to whether narrowband UVB delivered in the home would be cost effective.
- One partially applicable study with very serious limitations found that in a population with mild to moderate psoriasis, oral PUVA is more costly and more effective than broadband UVB with an ICER of £20 per additional day in remission. This was roughly translated to an incremental cost per QALY ratio of £39,167.
- One partially applicable study with very serious limitations found that in a population with moderate to severe psoriasis, oral PUVA is more costly and more effective than narrowband UVB with an ICER of £67 per additional 1% of patients achieving a PASI 75 or total body clearance. Based on this evidence alone, it is impossible to conclude whether PUVA would represent a more or less cost-effective use of NHS resources compared to narrowband UVB.

9.2 Recommendations and link to evidence

Recommendations on phototherapy	**58. Offer narrowband ultraviolet B (UVB) phototherapy to people with plaque or guttate-pattern psoriasis that cannot be controlled with topical treatments alone. Treatment with narrowband UVB phototherapy can be given three or two times a week depending on patient preference. Tell people receiving narrowband UVB that a response may be achieved more quickly with treatment three times a week.** **59. Offer other second or third line treatment options when:** • **narrowband UVB phototherapy results in an inadequate response or is poorly tolerated or** • **there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or**

	• **accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or** • **the person is at especially high risk of skin cancer.** **60. Consider psoralen[w] (oral or topical) with local ultraviolet A (UVA) irradiation to treat palmoplantar pustulosis.** **61. Do not routinely use phototherapy (narrowband UVB, broadband UVB or psoralen plus ultraviolet A [PUVA]) as maintenance therapy.** **62. Ensure that all phototherapy equipment is safety-checked and maintained in line with local and national policy[x].** **63. Healthcare professionals who are giving phototherapy should be trained and competent in its use and should ensure an appropriate clinical governance framework is in place to promote adherence to the indications for and contraindications to treatment, dosimetry and national policy on safety standards for phototherapy[y].**
Future research recommendations	**13. What are the efficacy, safety and cost effectiveness of NBUVB compared to oral/topical PUVA in the treatment of palmoplantar pustulosis?** **14. What are the long term risks (for example skin cancer, aging) of NBUVB , are there any individuals at particular risk and what strategies can be used to modify or avoid these risks?**
Relative values of different outcomes	The outcomes considered for this question were: • PASI75 • PASI50 • Change in PASI • Clear or nearly clear • Improved (for palmoplantar pustulosis population only) • Time to relapse (loss of PASI50) • Time to remission / maximum response • Change in DLQI • Burn • Cataracts • Severe adverse events

[w] At the time of publication (May 2012), psoralens did not have UK marketing authorisation for this indication in children. Informed consent should be obtained and documented.

x See: http://www.bad.org.uk/Portals/_Bad/Clinical%20Services/BAD%20Working%20Party%20Report%20on%20Phototherapy%20Services%202011v8%20final%20draft.pdf

[y] See: http://www.bad.org.uk/Portals/_Bad/Clinical%20Services/BAD%20Working%20Party%20Report%20on%20Phototherapy%20Services%202011v8%20final%20draft.pdf

	• Withdrawal due to toxicity The GDG considered which outcomes were most important when formulating recommendations for this review question. It was noted that it would be helpful to have consistency with the outcomes prioritised for the question on systemic non-biological therapies. Trials for phototherapy tend to report time to clearance, whereas trials for systemic non-biological therapies tend to report PASI75 or PASI50. Clear or nearly clear is a key outcome from the patient perspective, and there was most evidence for this outcome. Time to relapse and time to remission were felt to be important, as phototherapy is given intermittently, and so a longer duration of action is beneficial. There was no evidence for change in DLQI, cataracts or severe adverse events. The GDG discussed measures of toxicity. Toxicity from cumulative UV exposure was felt to be an inappropriate measure of toxicity, due to known inconsistencies in the metering of UV dose between centres. Number of treatments could be used instead of cumulative dose, but this was not an outcome for this question (although it is an outcome for the skin cancer question). Very few trials followed up participants at six or twelve months. There was no data on serious adverse events, so the GDG agreed on withdrawal due to toxicity as a measure of toxicity. There was limited evidence for the rest of the outcomes. Therefore the outcomes prioritised by the GDG were: • clear / nearly clear • time to relapse • time to remission • withdrawal due to toxicity
Trade off between clinical benefits and harms	The phototherapy efficacy data were considered in the context of adverse effects in the short term (in this evidence review) and also for longer term skin cancer risk (see section 9.7). UVB (either NBUVB or BBUVB) were effective for inducing remission for plaque and guttate psoriasis, and well tolerated in the short term. Only very limited data were available for skin cancer risk. There was no statistically significant benefit of NBUVB over BBUVB in terms of efficacy but a trend favouring NBUVB over BB UVB for clearance at the end of treatment. NBUVB three times a week is as effective as NBUVB twice a week, although time to clearance is shorter with three times weekly. The GDG agreed that either dosing schedule could be used depending on patient preference. Following treatment with UVB, most patients relapse. Time to relapse is variable. In patients who relapse rapidly, the time, inconvenience, cost incurred when multiple courses of UVB are required to maintain disease control, together with the potential aging and any (unknown) risk of skin cancer, mean that further courses of UVB may not be appropriate and other alternative treatments considered.

	PUVA is more effective than NBUVB for achieving clearance of plaque psoriasis when both are used twice a week, but the two interventions are comparable when NBUVB is given three times a week. For people with palmoplantar pustulosis, oral PUVA was effective in terms of clearance compared to no treatment. There is a trend towards topical PUVA being more effective than NBUVB, but this was not statistically significant. From the evidence it is not known whether topical PUVA is as good as oral PUVA, as this comparison was not made. Taking all the evidence into account, the risks of skin cancer with PUVA for psoriasis are significant, so UVB should be used in preference to PUVA as a first line phototherapy intervention. In patients who fail UVB, PUVA could be considered but only subject to the caveats and considerations discussed in section 9.7.
Economic considerations	There was limited health economic evidence to inform the GDG on the cost-effectiveness of BBUVB, NBUVB and PUVA. The GDG considered the partially applicable evidence whilst being mindful of its various methodological limitations. Two studies showed that PUVA was more costly and slightly more effective than broadband and narrowband UVB, but because neither study measured outcomes in terms of QALYs, the relative cost-effectiveness of PUVA remains indeterminable. When the result of one study was roughly translated from additional days in remission to QALYs, the incremental cost-effectiveness of PUVA was nearly £40,000 per QALY gained compared to broadband UVB. The GDG considered whether de novo economic modelling would help to reduce uncertainty in the cost-effectiveness of phototherapy and PUVA, but concluded that it was unlikely to provide any additional information other than that which was already available. This was largely due to a lack of long term trial data and that fact that it would be difficult to robustly incorporate the risk of skin cancer into a model. In the absence of high quality, UK specific evidence, the GDG considered the unit cost of delivering phototherapy, for which NHS reference costs from 2010-11 indicate that PUVA is £59 more costly per session compared to UVB. The clinical evidence suggests that there is very little difference in terms of effect (i.e. proportion achieving clearance of their psoriasis) between narrowband UVB administered at different frequencies (2x, 3x or 5x weekly). The main differences in effect appear to be related to the time and number of exposures by which clearance is achieved. The evidence suggests that increased frequency of exposures per week may result in a few more exposures (non-significant trend) and quicker clearance. This would translate to potentially higher costs, but also more QALYs. The combination of a vitamin D or vitamin D analogue to narrowband UVB may reduce the total number of exposures required to induce clearance, but the results did not reach statistical or clinical significance. The clinical evidence suggested that PUVA, if offered at the same frequency, may be slightly better than narrowband UVB in terms of the proportion achieving clearance, time to clearance and total exposures

	to clear. In deciding to recommend narrowband UVB over PUVA, the GDG considered that the cost of delivering PUVA is £59 more per session than narrowband UVB. If 24 sessions (2x weekly for 12 weeks or 3x weekly for 8 weeks) were required to induce response, treatment costs would amount to an extra £1,416 for PUVA compared to UVB; to be considered cost saving compared to narrowband UVB, PUVA would need to generate the same response in 14 sessions or less. Combined with the evidence that the longer term risks of skin cancer associated with PUVA appear to be high and potentially higher than with narrowband UVB, they concluded that PUVA was unlikely to represent better value for NHS resource than narrowband UVB. The GDG considered whether they should make a recommendation for phototherapy delivered in the home, given that clinical and cost-effectiveness evidence from the Netherlands suggested that it might be cost-effective. There were some concerns about the study and its application to decision-making for the NHS, including the inclusion of direct and indirect costs (productivity losses and travelling expenses) and the method by which QALYs were estimated during follow-up. The GDG was aware of home phototherapy being delivered in certain regions of the country, but did not consider the evidence robust enough to support its implementation across the entire NHS. In the end, the GDG recommended that it should only be considered in a select group of patients who may be unable to access hospital based services.
Quality of evidence	The GDG had reservations about the validity of the evidence comparing NB UVB and BB UVB, because some of the studies used BBUVB UV6, which is not true BBUVB as its wavelength lies somewhere between BBUVB and NBUVB. The Cameron study found that NBUVB three times a week is better than NBUVB two times a week, but the data could not be included in the meta analysis (because the standard deviation was not available and mean time-to-event data cannot be used). The GDG noted that NBUVB treatment regimes were likely to be sub-optimal in some studies owing to a low treatment frequency.
Other considerations	It was noted that in many departments, NBUVB had become the main form of UVB phototherapy. The GDG considered the evidence (for superior efficacy or safety of NBUVB over BBUVB) not strong enough to recommend disinvesting in BBUVB, and also noted that BBUVB was used for other dermatoses. The GDG considered home UVB treatment. The consensus view was that home UV treatment should be made available to people who are unable to access hospital treatment due to physical impairment or geographical reasons and when other treatment options have failed or could not be used. However given the unknown costs and lack of HE evidence the GDG were unable to make a national recommendation. From the GDG clinical knowledge PUVA itch and or pain is associated with PUVA use and can continue two years after stopping therapy. It

	affects up to 20% of patients. The GDG noted that phototherapy is absolutely contraindicated in certain groups of people (for example xeroderma pigmentosum other skin tumour prone photogenodermatoses), those with photosensitive dermatoses (for example lupus erythrematosus, particularly systemic type). There are also a number of relative contraindications (for example epilepsy). The GDG agreed that provision of an exhaustive list was beyond the scope of the guideline and that a recommendation that encompassed the fact that HCP should be aware of the indications and contraindications to phototherapy, and the optimal administration of phototherapy would be more appropriate. The GDG noted that the response rates for PPP in the PUVA versus NBUVB study were potentially clinically relevant when considering response rates documented in the placebo controlled PUVA studies; this condition is difficult to treat, often functionally disabling, and NBUVB is a well tolerated intervention. The GDG considered the use of NBUVB an area for future research.

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9.3 Phototherapy combined with acitretin

Phototherapy combination treatments usually involve topical anti- psoriasis therapies. For a minority of people with psoriasis, acitretin may be used in combination prior to, during and following a course of UVB or PUVA. Acitretin, a second generation retinoid, can be used as a monotherapy for psoriasis although the combination with phototherapy is generally conducted in the belief that it may reduce the number of phototherapy treatments, and thereby long term adverse effects. In addition, acitretin maintenance therapy is thought to delay disease relapse.

The GDG agreed to ask the following question: In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of acitretin plus UVB (NBUVB and BBUVB) and acitretin plus PUVA compared with their monotherapies and compared with each other?

9.3.1 Methodological introduction

A literature search was conducted for RCTs or systematic reviews that compared the efficacy and safety of acitretin plus UVB (narrowband or broadband) and acitretin plus PUVA compared with their monotherapies and compared with each other in people with psoriasis. No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded. Etretinate (Tigason) was excluded from the search as it is no longer used due to its longer half life (which is further prolonged with the consumption of alcohol) compared to acitretin.

The outcomes considered were:

- Clear or nearly clear (minimal residual activity/PASI>90/mild on PGA)
- PASI75
- PASI50
- Change in PASI (mean improvement)
- Time to relapse
- Time to remission/maximum response (treatment duration)
- Change in DLQI
- Burns (grade 3 erythema or grade 2 erythema with >50% BSA involved)
- Cataracts
- Number of UV treatments (as a surrogate for cumulative dose)
- Withdrawals due to drug toxicity
- Serious adverse events

Regarding the outcome of cataracts, most studies reported that participants wore protective goggles and no data on the event rate for cataracts were reported.

Six RCTs were found that addressed the question and were included in the review[275,278-282]. One of these studies used a within-patient randomisation design[275] and individual patient data were reported, which allowed the calculation of the appropriate standard error, accounting for the correlation of paired data. Note that no studies were available that assessed phototherapy combined with acitretin in an exclusively paediatric population.

9.3.12 Acitretin vs Acitretin plus BBUVB

9.3.221 Evidence profile

Table 94: Evidence profile comparing acitretin vs acitretin plus BBUVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acitretin plus UVB	Acitretin	Relative (95% CI)	Absolute	
Clear/ nearly clear on IAGI (>95%) (follow-up mean 6.3 weeks; maximum 30 exposures)											
1 lest 1989	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/9 (66.7%)	0%	RR 13 (5.84 to 28.94)	-	⊕⊕OO LOW
Withdrawal due to drug toxicity (follow-up mean 6.3 weeks; maximum 30 exposures)											
1 lest 1989	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/9 (11.1%)	1/9 (11.1%)	RR 1 (0.07 to 13.64)	0 fewer per 1000 (from 103 fewer to 1000 more)	⊕OOO VERY LOW

(a) Unblinded, unclear allocation concealment and method of randomisation and unclear baseline comparability for skin type and disease severity (symmetry of the psoriasis not stated)
(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as the line of no effect.

9.3.272 Evidence statements

In patients with psoriasis, acitretin plus BBUVB was statistically significantly better than acitretin for:

- Clear/nearly clear on IAGI after a maximum of 30 exposures [1 study; 9 participants (18 randomised units); low quality evidence][275]

In patients with psoriasis, there was no statistically significant difference between acitretin and acitretin plus BBUVB for:

- Withdrawal due to drug toxicity after a maximum of 30 exposures [1 study; 9 participants (18 randomised units); very low quality evidence][275]

9.3.13 Acitretin plus BBUVB vs placebo plus BBUVB

9.3.321 Evidence profile

Table 95: Evidence profile comparing acitretin plus BBUVB vs placebo plus BBUVB

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acitretin plus BBUVB	Placebo plus BBUVB	Relative (95% CI)	Absolute	
Clear/ nearly clear on IAGI (follow-up 8 weeks)											
1 Ruzicka 1990	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/40 (40%)	6/38 (15.8%)	RR 2.53 (1.11-5.79)	242 more per 1000 (from 17 more to 756 more)	⊕⊕OO LOW
Withdrawal due to drug toxicity (follow-up 8 weeks)											
1 Ruzicka 1990	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/34 (8.8%)	2/32 (6.3%)	RR 1.41 (0.25 to 7.91)	26 more per 1000 (from 47 fewer to 432 more)	⊕OOO VERY LOW

(a) Unclear allocation concealment, method of randomisation and drop out rates were unclear.
(b) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as the line of no effect

9.3.372 Evidence statements

In patients with psoriasis, there was a statistically significant difference favouring the use of acitretin plus BBUVB compared to a placebo plus BBUVB for:

- Clear/nearly clear on IAGI at 8 weeks [1 between-patient study; 78 participants; low quality evidence][278]

In patients with psoriasis, there was no statistically significant difference between acitretin plus BBUVB and placebo plus BBUVB for:

- Withdrawal due to drug toxicity at 8 weeks [1 between-patient study; 66 participants; very low quality evidence][278]

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9.3.24 Acitretin plus NBUVB vs acitretin plus PUVA

9.3.431 Evidence profile

4 **Table 96: Evidence profile comparing acitretin plus NBUVB vs acitretin plus PUVA**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acitretin plus NBUVB	Acitretin plus PUVA	Relative (95% CI)	Absolute	
PASI75 (follow-up 8 weeks)											
1 Ozdemir 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	17/30 (56.7%)	19/30 (63.3%)	RR 0.89 (0.59 to 1.35)	70 fewer per 1000 (from 260 fewer to 222 more)	⊕⊕OO LOW
PASI50 (follow-up 8 weeks)											
1 Ozdemir 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[b]	none	21/30 (70%)	23/30 (76.7%)	RR 0.91 (0.67 to 1.24)	69 fewer per 1000 (from 253 fewer to 184 more)	⊕⊕⊕O MODERATE
Number of UV treatments (follow-up 8 weeks; Better indicated by lower values)											
1 Ozdemir 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	Serious2	none	30	30	-	MD 0.3 higher (2.66 lower to 3.26 higher)	⊕⊕⊕O MODERATE
Maintenance of remission at 3 months											

Quality assessment							Summary of findings				
1 Ozdemir 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/17 (100%)	19/19 (100%)	RR 1.00 (0.9 to 1.11)	0 fewer per 1000 (from 100 fewer to 110 more)	⊕⊕⊕⊕ HIGH
Burns (follow-up 8 weeks)											
1 Ozdemir 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	1/30 (3.3%)	0/30 (0%)	RR 3 (0.13 to 70.83)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW
Withdrawal due to drug toxicity (follow-up 8 weeks)											
1 Ozdemir 2008	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[a]	none	1/30 (3.3%)	2/30 (6.7%)	RR 0.5 (0.05 to 5.22)	33 fewer per 1000 (from 63 fewer to 281 more)	⊕⊕OO LOW

(a) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as the line of no effect.
(b) Confidence interval ranges from a clinically important effect to no effect.

9.3.442 Evidence statements

In patients with psoriasis, there was no statistically significant difference between acitretin plus NBUVB and acitretin plus PUVA for:

- PASI 75 at 8 weeks [1 between-patient study; 60 participants; low quality evidence] [279]
- PASI50 at 8 weeks [1 between-patient study; 60 participants; moderate quality evidence][279]
- Number of UV treatments after a maximum of 8 weeks [1 between-patient study; 60 participants; moderate quality evidence] [279]
- Maintenance of remission at 3 months [1 between-patient study; 36 participants; high quality evidence] [279]
- Burns at 8 weeks [1 between-patient study; 60 participants; low quality evidence] [279]
- Withdrawal due to drug toxicity at 8 weeks [1 between-patient study; 60 participants; low quality evidence] [279]

The data for the number of UV treatments was not reported clearly. The figures given were assumed to be a standard deviation rather than a standard error of the mean. If using the SEM the SD would have been greater than the mean number of UV treatments.

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9.3.5 Acitretin plus PUVA vs placebo plus PUVA

9.3.5.1 Evidence profile

4 **Table 97: Evidence profile comparing acitretin plus PUVA vs placebo plus PUVA.**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acitretin plus PUVA	Placebo plus PUVA	Relative (95% CI)	Absolute	
Clear/ nearly clear on IAGI (follow-up 8-12 weeks)											
3 Saurat 1998 Sommerburg 1993 Tanew 1991	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	67/81 (82.7%)	55/88 (62.5%)	RR 1.33 (1.11 to 1.59)	206 more per 1000 (from 69 more to 369 more)	⊕OOO VERY LOW
Time to remission (follow-up 12 weeks; Better indicated by lower values)											
1 Saurat 1998	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	22	-	MD 17.60 lower (26.02 to 9.18 lower)	⊕⊕⊕O MODERATE
Mean number of UV treatments (all participants) (follow-up 8 weeks; Better indicated by lower values)											
1 Sommerburg 1993	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	43	-	MD 0.2 higher (2.58 lower to 2.98 higher)	⊕⊕OO LOW
Mean number of UV treatments - Number of UVA treatments (among those who cleared) (follow-up 11-12 weeks; Better indicated by lower values)											
2 Saurat 1998 Tanew 1991	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	45	-	MD 6.17 lower (9.2 to 3.14 lower)	⊕⊕⊕O MODERATE
Withdrawal due to toxicity (follow-up 8-12 weeks)											
3 Saurat 1998 Sommerburg 1993	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[f]	none	7/81 (8.6%)	4/78 (5.1%)	RR 1.58 (0.51 to 4.87)	30 more per 1000 (from 25 fewer to 198 more)	⊕OOO VERY LOW

Tanew 1991											
Severe adverse events (follow-up 12 weeks)											
2 Saurat 1998 Sommerburg 1993	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/60 (25%)	4/65 (6.2%)	RR 4.11 (1.55 to 10.92)	191 more per 1000 (from 34 more to 610 more)	⊕⊕⊕O MODERATE

(a) 3/3 allocation concealment and method of randomisation; 2/3 (total 70% weighting) had a high drop out rate 20% TANEW and 23.9% SOMMERBURG.
(b) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(c) Unclear allocation concealment. No information on the method of randomization, previous treatment history or the use of concurrent treatments during the trial.
(d) Unclear allocation concealment and randomisation method and high drop out rate (23.9%).
(e) 2/2 studies had unclear allocation concealment and method of randomisation; 1/2 had a 20% drop out rate.
(f) Confidence interval crosses the boundary for clinical significance in favour of both treatments, as well as the line of no effect.
(g) 2/2 unclear allocation concealment and method of randomization Drop out rate was 23.9% in one study (25% weighted)

9.3.582 Evidence statements

In patients with psoriasis, there was a statistically significant difference favouring the use of acitretin plus PUVA compared to placebo plus PUVA for the:

- Clear/ nearly clear on IAGI at 8-12 weeks [3 between-patient studies; 169 participants; very low quality evidence] [280-282]
- Mean number of UV treatments (studies using a Completers Analysis) after a maximum of 8 weeks [2 between-patient studies; 86 participants; moderate quality evidence] [281,282]
- Time to remission after a maximum of 12 weeks [1 between-patient study; 33 participants; moderate quality evidence][281]

A statistically significant difference favouring the use of a placebo plus PUVA compared to acitretin plus PUVA was found for:

- Severe adverse events at 12 weeks [2 between-patient studies; 125 participants; moderate quality evidence] [280,281].

No statistically significant associations were found for:

- Withdrawal due to drug toxicity at 8-12 weeks [3 between-patient studies; 159 participants; very low quality evidence] [280-282])
- Mean number of UV treatments after a maximum of 8 weeks [1 between-patient study; 83 participants; low quality evidence] [280]

9.3.513 Heterogeneity

There was heterogeneity between the three studies for the outcome of number of UV treatments. The studies did not report the mean number of UVB treatments require for clearance in those who achieved remission but rather the total mean number in the analysis set; however, those who achieved remission before the end of the study did stop treatment early. It is likely that this was because the Sommerburg study included all patients randomised while the other two studies only reported an available case analysis, but it could also have been due to the higher proportion of people in the Sommerburg study with non-plaque type psoriasis: both the Tanew and Saurat studies had primarily patients with chronic plaque psoriasis (100% and 93% respectively) whereas Sommerburg had a mixed population (acitretin arm: guttate 12.5%, nummular 27.5%, plaque 57.5%, guttate and nummular 2.5%; placebo arm: guttate 9.3%, nummular 23.3%, plaque 65.1%, guttate and nummular 2.3%)- figures are acitretin plus PUVA and placebo plus PUVA respectively. The lower proportion with plaque psoriasis in the acitretin arm could have meant that the psoriasis was more resistant and took relatively longer to clear than that in the placebo arm.

9.3.6 Economic evidence

An economic evaluation should ideally compare all relevant alternatives. No studies were identified comparing all interventions of interest –acitretin, narrowband UVB, PUVA and combinations of acitretin and narrowband UVB or PUVA – in the treatment of patients with psoriasis.

1 study [273] was included that compared acitretin, narrowband UVB and PUVA . These results are summarised in the economic evidence profile below (Table 98 and Table 99). See also the full study evidence tables on in Appendix I.

One study [274] comparing acitretin, PUVA and combined acitretin and PUVA (RePUVA) was excluded due to its poor applicability and very serious methodological limitations (see Appendix G).

No relevant economic evaluations comparing acitretin, narrowband UVB or combined acitretin and narrowband UVB were identified.

Table 98: Acitretin versus Narrowband UVB versus PUVA – Economic study characteristics

Study	Limitations	Applicability	Other comments
Pearce (2006)[273]	Very serious limitations (a)	Partially applicable (b)	Simple decision analytic model; treatment effects estimated as a weighted mean probability of PASI 75 response from Kragballe 1989[283], Gordon 1999[263] and an unknown reference

(a) 12-week time horizon may be insufficient to evaluate effectiveness of interventions and capture consequences of treatment failures; treatment effects estimated from an unadjusted indirect comparison from a systematic review of RCT evidence; no sensitivity analyses reported; funded by Galderma Laboratories

(b) Some uncertainty about applicability of US clinical practice, estimates of resource use and unit costs; QALYs not used.

Table 99: Acitretin versus Narrowband UVB versus PUVA – Economic summary of findings (Pearce 2006)

Interventions	Incremental cost (compared to next most costly intervention)	Incremental effects (compared to next most costly intervention)	ICER	Uncertainty

Interventions	Incremental cost (compared to next most costly intervention)	Incremental effects (compared to next most costly intervention)	ICER	Uncertainty
Acitretin (25 mg/day)	NA	NA		A series of deterministic sensitivity analyses were performed, but effect on base case results could not be determined from the report.
Narrowband UVB	£794	20% more participants achieving PASI75 or total body clearance	£40 per additional 1% achieving PASI75 or total body clearance	A series of deterministic sensitivity analyses were performed, but effect on base case results could not be determined from the report.
PUVA	£810	12% more participants achieving PASI75 or total body clearance	£67 per additional 1% achieving PASI75 or total body clearance	A series of deterministic sensitivity analyses were performed, but effect on base case results could not be determined from the report.

Pearce (2006) used the proportion of participants achieving a PASI75 or total body clearance as their primary outcome measure. The 12-week time horizon of the analysis should be considered a significant limitation because it is not sufficiently long enough to capture the true effects of the interventions being evaluated, nor is it long enough to account for the costs and consequences of participants who do not achieve a PASI75 or total body clearance.

It is also worth noting that the analysis included systemic non-biological therapies –ciclosporin, methotrexate – as comparators. Looking at the overall results, acitretin was dominated (more costly and less effective than) by methotrexate, narrowband UVB was dominated by ciclosporin, and PUVA was more costly and more effective than ciclosporin with an ICER of £934 per additional 1% achieving PASI75 or total body clearance.

9.3.6.11 Evidence statements

- One partially applicable study with very serious limitations found that in a population with moderate to severe psoriasis, narrowband UVB is more costly and more effective than acitretin (25 mg/day), with an ICER of £40 per additional 1% achieving PASI75 or total body clearance. However, based on this evidence alone, it is unclear whether this represents good value for the UK NHS.
- One partially applicable study with very serious limitations found that in a population with moderate to severe psoriasis, oral PUVA is more costly and more effective than narrowband UVB with an ICER of £67 per additional 1% of patients achieving a PASI 75 or total body clearance. Based on this evidence alone, it is impossible to conclude whether PUVA would represent a more or less cost-effective use of NHS resources compared to narrowband UVB.

9.4 Recommendations and link to evidence

Recommendations on phototherapy	**64. Do not routinely offer co-therapy with acitretin when administering PUVA.**

Future research recommendations	**15. In people with psoriasis, what is the clinical effectiveness, safety, tolerability and cost effectiveness of NBUVB phototherapy and acitretin versus acitretin and placebo?**
Relative values of different outcomes	The outcomes considered for this question were: • PASI75 • PASI50 • Change in PASI • Clear or nearly clear • Improved (for palmoplantar pustulosis population only) • Time to relapse (loss of PASI50) • Time to remission / maximum response • Change in DLQI • Burn • Cataracts • Severe adverse events • Withdrawal due to toxicity • Number of UV treatments (surrogate for cumulative dose). There was no data for DLQI or cataracts.
Trade off between clinical benefits and harms	• The GDG did not feel that there was sufficient evidence that the clinical benefit of taking acitretin is outweighed by the risks and side effects associated with acitretin. The data suggest that adding acitretin to PUVA may increase efficacy and reduce the number of UV exposures and time-to-remission; however, the data were not conclusive and in view of the high number of serious adverse events reported when adding acitretin to PUVA the GDG agreed that this adjunctive therapy should not be considered as standard practice. • Risk of hyperlipiaemia and there is already an increased risk of cardiovascular comorbidities among people with psoriasis. • A high dose is needed to be efficacious and adverse effects are associated with a higher dose.
Economic considerations	There was limited health economic evidence to inform the GDG on the cost-effectiveness of acitretin combined with either UVB or PUVA compared to any single therapy used alone. The GDG considered the partially applicable evidence whilst being mindful of its various methodological limitations. The published economic evidence showed that PUVA is more costly than both acitretin and narrowband UVB, but could not demonstrate whether its additional benefits, in terms of gains in quality of life, are worth the additional cost. Similarly, no economic evidence was available to indicate whether narrowband UVB with or without combined acitretin is more or less cost-effective than acitretin or PUVA or combined acitretin and PUVA. Given the uncertainties in the clinical and economic evidence, the

	GDG did not consider the potential gains of combining acitretin with UVB or PUVA to outweigh the risks and side effects associated with the drug.
Quality of evidence	• Small studies; sparse information about participants. • Most studies used etretinate instead of acitretin. Etretinate is converted to acitretin, so bioavailability and dosing is different to acitretin. Therefore studies using etretinate were excluded. • Data for key comparisons was not available: NBUVB vs. acitretin plus NBUVB, and acitretin vs. acitretin plus NBUVB. • The Saurat and Tanew studies analysed only the participants who completed the study. The Sommerburg study analysed all participants, but excluded those with missing data. The Sommerburg study included a mixed population, whereas Saurat and Tanew included primarily chronic plaque psoriasis. • All of the studies were unclear with respect to whether acitretin was continued after participants had reached clearance. The GDG assumed that acitretin was stopped when clearance was achieved. • The GDG noted the following variables among the studies: • Treatment frequency varied between the studies (PUVA and BBUVB varied from three to five times per week). • Acitretin dose varied between the studies (doses ranged from 24mg – 60mg based on a 60kg person). • Dose regime varied (some studies used a higher dose for the first / second week followed by a lower dose for the rest of the trial). • Length of follow up ranged from eight and 12 weeks. • One small study (nine participants) was included for the comparison of acitretin vs. acitretin plus BBUVB. The frequency of BBUVB exposure was unclear and there was no information on previous acitretin use, skin type or symmetry of psoriasis and therefore a high risk of bias. Small numbers, very low quality and serious / very serious imprecision. • One study was included for the comparison of acitretin plus BBUVB vs. placebo plus BBUVB (78 participants). Skin type was not reported. It was difficult to identify the number of participants who dropped out, as there was a discrepancy between the number of reported drop outs and the number of participants for whom data was reported. • One study was included for the comparison of acitretin plus NBUVB vs. acitretin plus PUVA – this was a high quality study. • Three studies were included for acitretin plus PUVA vs. placebo plus PUVA on the outcome of number of treatments. High heterogeneity was noted, which could be due to the type of analysis or methodology used in one of the studies (Sommerburg). • There were no data for NBUVB and acitretin vs. NBUVB alone. Therefore the GDG were unable to assess the benefit of adding

	acitretin to NBUVB.
Other considerations	• The GDG noted that acitretin should not be used in women of child bearing age and should not be used for longer than three years. • The addition of acitretin to phototherapy can be considered for people with psoriasis although this should not be routinely offered owing to the paucity of evidence.

9.5 Dithranol, coal tar and vitamin D or vitamin D analogues combined with UVB

The use of broad band UVB in conjunction with 24 hour applications of either dithranol (Ingram's regimen[284,285], usually administered over 4-6 weeks during inpatient based treatment cycles formed the mainstay of therapy for psoriasis for more than 50 years. More recently, these agents (also referred to as 'complex' topicals given that they require 'special manufacture[148] and training to use) have been used in a daycare setting, applied for just 1 or 2 hours (so called 'short contact' therapy) with improved patient acceptability and reduction in resource use, particularly inpatient care. This practice remains widespread in England and Wales[14].

This historical context is important, since it explains the generally held belief that the combination of topical anti-psoriatic agents with UVB will improve outcomes and reduce the duration of phototherapy and has led to the subsequent development of combination treatment regimens using modern interventions such as vitamin D or vitamin D analogues with narrow band UVB.

Therapy duration is a significant consideration for patients and providers. The inconvenience of repeat hospital visits include travel expense and time away from work which means that any combined topical treatment is attractive as a way of reducing the duration of a phototherapy course and reducing total UV exposure. However, some patients are keen to avoid using topical treatments during phototherapy, many patients have been using “messy” topicals previously and particularly value a spell off topical treatment. There is also evidence that certain ointment-based topical treatments can block UV and may therefore reduce the efficacy of phototherapy.

Administration of 'complex topicals' is also time consuming and health care resource use intensive. Individual patient preferences and clinical practice therefore vary.

The GDG therefore considered it important to review the evidence on the clinical effectiveness, safety, tolerability and cost effectiveness of UVB combined with dithranol, coal tar or vitamin D and vitamin D analogues compared with UVB alone to investigate the clinical benefit of these topical interventions in conjunction with UVB, and whether they are appropriate in the context of the other therapies that are now available.

9.5.1 Methodological introduction

A literature search was conducted for RCTs or systematic reviews that compared the efficacy and safety of UVB phototherapy used in combination with topical therapies compared with UVB alone or topical therapy alone in people with psoriasis. No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The outcomes considered were:

- PASI75
- PASI50
- Change in PASI (mean improvement)
- Clear or nearly clear (minimal residual activity/PASI>90/mild on PGA)
- Time-to-relapse
- Time to remission/max response
- Change in DLQI

- Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved)
- Cataracts
- Number of UV treatments (as a surrogate for cumulative dose)

Note that narrow band and broad band UVB were stratified a priori, as they are considered to be substantially different reagents.

Thirteen RCTs[286-298] were identified that addressed the question and were therefore included in the review. Note that no studies were available that assessed phototherapy combined with topical treatments in an exclusively paediatric population.

Four of the studies[287,288 295,297] were designed as within-patient comparisons. It was recognised that data from within-patient trials should be adjusted for the correlation coefficient relating to the comparison of paired data. However, none of the included studies reported this statistic and only one reported sufficient detail for it to be calculated (for the outcome of clear/nearly clear) [295].

9.5.12 Vitamin D analogue plus NBUVB vs vitamin D analogue alone

9.5.2.1 Evidence profile

Table 100: Evidence profile comparing vitamin D analogue plus NBUVB vs vitamin D analogue alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D analogue + NBUVB	Vitamin D analogue alone	Relative (95% CI)	Absolute	
Clearance (PASI100) - calcipotriol (follow-up 3 months)											
1 Roussaki-Schulze 2005	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/15 (13.3%)	4/15 (26.7%)	RR 0.5 (0.11 to 2.33)	133 fewer per 1000 (from 237 fewer to 355 more)	⊕OOO VERY LOW
PASI 50 - calcipotriol (follow-up 3 months)											
1 Roussaki-Schulze 2005	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	12/15 (80%)	6/15 (40%)	RR 2 (1.02 to 3.91)	400 more per 1000 (from 8 more to 1000 more)	⊕OOO VERY LOW
Mean reduction in PASI - calcipotriol (follow-up 3 months; Better indicated by higher values)											
1 Roussaki-Schulze 2005	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[d]	none	15	15	-	MD 1.98 higher (0.82 to 3.14 higher)	⊕OOO VERY LOW
Change in PASI - calcipotriol (follow-up 3 months; Better indicated by higher values)											
1 Bourke 1997	randomised trials	very serious[e]	no serious inconsistency	no serious indirectness	serious[f]	none	15	15	-	UVB + calcipotriol / Calcipotriol alone Baseline 14.6 / 11.7 4 weeks 3.4* / 6.3	⊕OOO VERY LOW
Change in PASI - tacalcitol (follow-up 3 weeks; better indicated by higher values)											

1 Rocken 1998	randomised trials	very serious[g]	no serious inconsistency	no serious indirectness	serious[f]	none	22	22	-	Tacalcitol + NBUVB / Tacalcitol Baseline 14.09 / 14.09 3 weeks 4.25 / 7.03 Final PASI SS lower in combined group (p<0.001)	⊕OOO VERY LOW
Withdrawal due to adverse events - Tacalcitol (follow-up 3 weeks)											
1 Rocken 1998	randomised trials	very serious[g]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	0/22 (0%)	RR 2.88 (0.12 to 67.03)	-	⊕OOO VERY LOW

(a) Unclear method of randomisation, no allocation concealment, unblinded and not matched at baseline for PASI score (difference greater in magnitude than the mean difference change during the study)
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(d) Confidence interval ranges from clinically important effect to no effect
(e) Unclear method of randomisation, no allocation concealment, unblinded
(f) No measure of variance available
(g) Unclear method of randomisation and allocation concealment, unblinded

9.5.2.2 Evidence statements

In people with psoriasis, calcipotriol combined with NBUVB was statistically significantly better than calcipotriol alone for:

- PASI 50 at 3 months [1 between-patient study, 30 participants, very low quality evidence][286]
- Mean reduction in PASI at 3 months [1 between -patient study, 30 participants, very low quality evidence][286]

In people with psoriasis, there was no statistically significant difference between vitamin D analogues combined with NBUVB versus vitamin D analogue alone for:

- Clearance (PASI100) at 3 months for calcipotriol [1 between -patient study, 30 participants, very low quality evidence][286]
- Withdrawal due to adverse events for tacalcitol [1 within-patient study, 23 participants (45 randomised units), very low quality evidence][287]

Evidence statements for individual studies where no original analysis could be performed comparing vitamin D analogue plus NBUVB versus vitamin D analogue alone:

- Mean PASI improved significantly more at 3 months with calcipotriol combined with NBUVB versus calcipotriol alone [1 between -patient study, 30 participants, very low quality evidence][292]

- Mean final PASI at 3 weeks was a statistically significantly lower with tacalcitol combined with NBUVB versus tacalcitol alone [1 within-patient study, 22 participants (44 randomised units), very low quality evidence][287]

9.5.33 Calcipotriol plus BBUVB vs calcipotriol

9.5.341 Evidence profile

Table 101: Evidence profile comparing calcipotriol plus BBUVB vs calcipotriol

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcipotriol + BBUVB	Calcipotriol	Relative (95% CI)	Absolute	
Clearance (follow-up 8 weeks)											
1 Kragballe 1990	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7/18 (38.9%)	3/18 (16.7%)	RR 2.33 (0.71 to 7.63)	222 more per 1000 (from 48 fewer to 1000 more)	⊕OOO VERY LOW

(a) Unclear method of randomisation, no allocation concealment, unblinded
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect

9.5.352 Evidence statements

In people with psoriasis, there was no statistically significant difference between calcipotriol combined with BBUVB and calcipotriol alone for:

- Clearance at 8 weeks [1 within-patient study, 18 participants (36 randomised units), very low quality evidence][288]

9.5.14 Calcipotriol plus NBUVB vs placebo plus NBUVB

9.5.421 Evidence profile

Table 102: Evidence profile comparing calcipotriol plus NBUVB vs placebo plus NBUVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcipotriol + NBUVB	Placebo + NBUVB	Relative (95% CI)	Absolute	
Clearance (follow-up 6 weeks)											
1 Rim 2002	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	9/10 (90%)	11/18 (61.1%)	RR 1.47 (0.97 to 2.25)	287 more per 1000 (from 18 fewer to 764 more)	⊕OOO VERY LOW
Percentage change in PASI (follow-up unclear; Better indicated by higher values)											
1 Brands 1999	randomised trials	very serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	25	28	-	MD 3.8 higher (21.67 lower to 29.27 higher)	⊕OOO VERY LOW
Change in PASI (follow-up 20 sessions (6.7 weeks); Better indicated by higher values)											
1 Woo 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 2 higher (1.8 lower to 5.8 higher)	⊕⊕⊕⊕ HIGH
Change in PASI (follow-up 3 months; Better indicated by higher values)											
1 Bourke 1997	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[e]	none	15	15	-	UVB + Vit D / UVB alone Baseline 14.6 / 12.0 4 weeks 3.4 / 7.5	⊕OOO VERY LOW
Mean number of UVB treatments - trunk (follow-up 6 weeks; Better indicated by lower values)											
1 Rim 2002	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	10	18	-	MD 1.4 lower (5.46 lower to 2.66 higher)	⊕OOO VERY LOW

Mean number of UVB treatments - extremities (follow-up 6 weeks; Better indicated by lower values)											
1 Rim 2002	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	10	18	-	MD 2.5 lower (5.97 lower to 0.97 higher)	⊕OOO VERY LOW
Mean number of UVB treatments (follow-up 6.7 weeks – one study unclear; Better indicated by lower values)											
2 Brands 1999 Woo 2003	randomised trials	no serious risk of bias[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	53	-	MD 1.59 lower (3.45 lower to 0.26 higher)	⊕⊕⊕⊕ HIGH
Mild to moderate burn (follow-up 6 weeks)											
1 Rim 2002	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/10 (20%)	2/18 (11.1%)	RR 1.8 (0.3 to 10.9)	89 more per 1000 (from 78 fewer to 1000 more)	⊕OOO VERY LOW
Withdrawal due to adverse events (follow-up 6-6.7 weeks – one study unclear)											
3 Brands 1999 Rim 2002 Woo 2003	randomised trials	serious[g]	serious[h]	no serious indirectness	very serious[d]	none	3/60 (5%)	2/71 (2.8%)	RR 1.65 (0.38 to 7.04)	18 more per 1000 (from 17 fewer to 170 more)	⊕OOO VERY LOW

(a) Unclear method of randomisation, no allocation concealment, unblinded
(b) Confidence interval ranges from clinically important effect to no effect
(c) Inadequate randomisation sequence, unclear allocation concealment and single blind
(d) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(e) No measure of variance available
(f) No serious limitations in study weighted 89%
(g) 2/3 (total 44.2% weighted) studies inappropriate randomisation, unclear allocation concealment and unclear/no blinding
(h) No statistical heterogeneity but point estimates suggest different directions of effect

9.5.492 Evidence statements

In people with psoriasis, there was no statistically significant difference between calcipotriol combined with NBUVB versus NBUVB plus placebo for:

- Clearance at 6 weeks [1 between-patient study, 28 participants, very low quality evidence] [289]
- Mean number of UVB treatments [2 between-patient studies, 103 participants, high quality evidence][290,291]

- Mean number of UVB treatments (extremities or trunk) [1 between-patient study, 28 participants, very low quality evidence][289]
- Percentage change in PASI [1 between-patient study, 53 participants, very low quality evidence][290]
- Change in PASI after a maximum of 20 sessions [1 between-patient study, 50 participants, high quality evidence][291]
- Mild to moderate burn at 6 weeks [1 between-patient study, 28 participants, very low quality evidence] [289]
- Withdrawal due to adverse events at 6 weeks or a maximum of 20 sessions [3 between-patient studies, 131 participants, very low quality evidence] [289-291]

Evidence statements for individual studies where no original analysis could be performed comparing vitamin D analogue plus NBUVB versus NBUVB alone:

- Mean PASI improved significantly more at 3 months with calcipotriol combined with NBUVB versus NBUVB alone [1 between-patient study, 30 participants, very low quality evidence] [292]

9.5.5 Vitamin D or vitamin D analogue plus BBUVB vs placebo plus BBUVB

9.5.5.1 Evidence profile

Table 103: Evidence profile comparing vitamin D or vitamin D analogue plus BBUVB vs placebo plus BBUVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D or vitamin D analogue + BBUVB	Placebo + BBUVB	Relative (95% CI)	Absolute	
Clear or nearly clear on IAGI - calcitriol (follow-up 8 weeks)											
1 Ring 2001	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/49 (44.9%)	11/53 (20.8%)	RR 2.16 (1.17 to 3.98)	241 more per 1000 (from 35 more to 618 more)	⊕⊕⊕O MODERATE
Clearance - calcipotriol (follow-up 3 months)											
1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c,d]	serious[e]	none	48/80 (60%)	51/79 (64.6%)	RR 0.93 (0.73 to 1.18)	45 fewer per 1000 (from 174 fewer to 116 more)	⊕OOO VERY LOW

Number of UV treatments for clearance (Cox proportional model) - Calcipotriol (follow-up 3 months)											
1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c]	no serious imprecision	Median number of treatments Combi: 22 (8-25) UVB: 25 (14-35)	48/80 (60%)	51/79 (64.6%)	RR 3.66 (2.16 to 6.2)	1000 more per 1000 (from 749 more to 1000 more)	⊕⊕OO LOW
Modified PASI 80 (excludes head) (follow-up 3 months)											
1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c]	serious[f]	none	61/80 (76.3%)	58/79 (73.4%)	RR 1.04 (0.87 to 1.24)	29 more per 1000 (from 95 fewer to 176 more)	⊕OOO VERY LOW
Number of UV treatments for modified PASI 80 - Calcipotriol (follow-up 3 months)											
1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c]	no serious imprecision	Median number of treatments Combi: 12 UVB:19	61/80 (76.3%)	58/79 (73.4%)	RR 2.59 (1.71 to 3.92)	1000 more per 1000 (from 521 more to 1000 more)	⊕⊕OO LOW
Percentage change in modified PASI - Calcipotriol (follow-up 3 months; Better indicated by higher values)											
1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c]	no serious imprecision	none	80	79	-	MD 3.1 lower (13.37 lower to 7.17 higher)	⊕⊕OO LOW
Percentage change in PASI - calcitriol (follow-up 8 weeks; Better indicated by higher values)											
1 Ring 2001	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[g]	none	49	53	-	MD 22% Combi: 65% UVB: 43%	⊕⊕OO LOW
Relapse rate post-treatment among clearers - Calcipotriol (follow-up 12 weeks post treatment)											
1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c]	very serious[h]	none	47	48	RR 0.81 (0.29 to 2.26)	-	⊕OOO VERY LOW
Burn/erythema/pruritus - Calcipotriol (follow-up 3 months)											

1 Ramsay 2000	randomised trials	serious[b]	no serious inconsistency	serious[c]	serious[e]	none	22/80 (27.5%)	33/79 (41.8%)	RR 0.66 (0.42 to 1.02)	142 fewer per 1000 (from 242 fewer to 8 more)	⊕OOO VERY LOW
Withdrawal due to adverse events - calcitriol (follow-up 8 weeks)											
1 Ring 2001	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[h]	none	2/49 (4.1%)	1/53 (1.9%)	RR 2.16 (0.2 to 23.11)	22 more per 1000 (from 15 fewer to 417 more)	⊕OOO VERY LOW

(a) Unclear method of randomisation, no allocation concealment
(b) No allocation concealment, single blinded
(c) Indirect comparison: the group with adjunctive topical therapy received UVB twice weekly but the UVB alone group visited three-time weekly for treatment
(d) Definition of clearance was complete resolution of psoriasis or requiring only emollients
(e) Confidence interval ranges from clinically important effect to no effect
(f) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(g) No measure of variance provided
(h) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect

9.5.592 Evidence statements

In people with psoriasis, there was a statistically significant difference favouring a vitamin D or vitamin D analogue combined with BBUVB versus BBUVB plus placebo for:

- Clear or nearly clear on IAGI at 8 weeks for calcitriol [1 between-patient study, 102 participants, moderate quality evidence][293]
- Number of UV treatments to clearance after a maximum follow-up of 3 months for calcipotriol [1 between-patient study, 159 participants, low quality evidence][294]
- Number of UV treatments to modified PASI80 after a maximum follow-up of 3 months for calcipotriol [1 between-patient study, 159 participants, low quality evidence][294]

In people with psoriasis, there was no statistically significant difference between vitamin D or vitamin D analogue combined with BBUVB versus BBUVB plus placebo for:

- Clearance at 3 months for calcipotriol [1 between-patient study, 159 participants, very low quality evidence] [294]
- Modified PASI 80 at 3 months for calcipotriol [1 between-patient study, 159 participants, very low quality evidence] [294]
- Percentage change in modified PASI at 3 months for calcipotriol [1 between-patient study, 159 participants, low quality evidence] [294]
- Relapse post-treatment among clearers after a maximum follow-up of 12 weeks post-treatment for calcipotriol [1 between-patient study, 95 participants, very low quality evidence] [294]

- Burn/erythema/pruritus at 3 months for calcipotriol [1 between-patient study, 159 participants, very low quality evidence] [294]
- Withdrawal due to adverse events at 8 weeks for calcitriol [1 between-patient study, 102 participants, very low quality evidence] [293]

Evidence statements for individual studies where no statistical analysis could be performed comparing vitamin D plus BBUVB versus placebo plus BBUVB:

- Percentage change in PASI at 8 weeks was greater with calcitriol compared with placebo [1 between-patient study, 102 participants, low quality evidence][293]

9.5.563 Heterogeneity

There was statistically significant heterogeneity between the two studies for the outcome of clear/nearly clear[293,294]. It was not possible to conclusively determine the cause of this inconsistency, which could have been due to different vitamin D agents being used, different definitions of response or different follow-up times

9.5.16 LCD (Liquor carbonis distillate; equiv. 2.3% coal tar) plus NBUVB vs NBUVB

9.5.621 Evidence profile

Table 104: Evidence profile comparing LCD (liquor carbonic distillate; equivalent 2.3% coal tar) plus NBUVB vs NBUVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LCD + NBUVB	NBUVB	Relative (95% CI)	Absolute	
Clearance (follow-up 12 weeks)											
1 Bagel 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7/12 (58.3%)	6/12 (50%)	RR 1.17 (0.56 to 2.45)	85 more per 1000 (from 220 fewer to 725 more)	⊕OOO VERY LOW
Moderate burn (follow-up 12 weeks)											
1 Bagel	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/12 (16.7%)	2/12 (16.7%)	RR 1 (0.17 to 5.98)	0 fewer per 1000 (from 138 fewer to 830 more)	⊕OOO VERY LOW

2009											
Withdrawals due to adverse events (follow-up 12 weeks)											
1 Bagel 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/12 (0%)	0/12 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Serious adverse events (follow-up 12 weeks)											
1 Bagel 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/12 (0%)	0/12 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Median weeks to clearance (follow-up 12 weeks; Better indicated by higher values)											
1 Bagel 2009	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	12	12	-	NBUVB + LCD: 4 weeks NBUVB: 7 weeks p-value: 0.187	⊕⊕OO LOW

(a) Unclear method of randomisation, no allocation concealment, partial blinding
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) No measure of variance provided

9.5.642 Evidence statements

In people with psoriasis, there was no statistically significant difference between LCD combined with NBUVB versus NBUVB for:

- Clearance at 12 weeks [1 within-patient study, 12 participants (24 randomised units), very low quality evidence][295]
- Moderate burn at 12 weeks [1 within-patient study, 12 participants (24 randomised units), very low quality evidence][295]

In people with psoriasis, there were no events with either LCD combined with NBUVB or NBUVB for:

- Withdrawal due to adverse events at 12 weeks [1 within-patient study, 12 participants (24 randomised units), moderate quality evidence][295]
- Serious adverse events at 12 weeks [1 within-patient study, 12 participants (24 randomised units), moderate quality evidence][295]

Evidence statements for individual studies where no original analysis could be performed comparing LCD plus NBUVB versus NBUVB:

- There was no statistically significant difference reported between the median number of weeks to clearance/minimal disease after a maximum follow-up of 12 weeks [1 within-patient study, 12 participants (24 randomised units), low quality evidence][295]

9.5.17 Tar oil plus sub-erythemogenic BB-VB vs placebo plus maximally erythemogenic BBUVB

9.5.721 Evidence profile

Table 105: Evidence profile comparing tar oil plus sub-erythemogenic BBUVB vs placebo plus maximally erythemogenic BBUVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tar oil + low dose BBUVB	Placebo + high dose BBUVB	Relative (95% CI)	Absolute	
Clearance (follow-up 12 weeks)											
1 Menkes 1985	randomised trials	very serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	19/30 (63.3%)	14/19 (73.7%)	RR 0.86 (0.59 to 1.26)	103 fewer per 1000 (from 302 fewer to 192 more)	⊕OOO VERY LOW
Mean number of treatments to clear (follow-up 12 weeks; Better indicated by lower values)											
1 Menkes 1985	randomised trials	very serious[a]	no serious inconsistency	serious[b]	serious[d]	none	19	14	-	MD 4 Tar: 17 Placebo: 21 P<0.05	⊕OOO VERY LOW

(a) No allocation concealment, unblended
(b) Groups received different doses of UVB
(c) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(d) No measure of variance reported

9.5.782 Evidence statements

In people with psoriasis, there was no statistically significant difference between tar oil with suberythemogenic BBUVB versus maximally erythemogenic BBUVB with placebo for:

- Clearance at 12 weeks [1 between-patient study, 49 participants, very low quality evidence] [296]

Evidence statements for individual studies where no original analysis could be performed comparing tar oil plus suberythemogenic BBUVB versus placebo plus maximally erythemogenic BBUVB:

- There was a statistically significant reduction in mean number of UVB treatments for clearance with tar oil + suberythemogenic BBUVB versus placebo + maximally erythemogenic BBUVB after a maximum follow-up of 12 weeks [1 between-patient study, 33 participants, very low quality evidence] [296]

9.5.8 Dithranol (Micanol) plus BBUVB vs Dithranol

9.5.8.1 Evidence profile

Table 106: Evidence profile comparing dithranol (micanol) plus BBUVB vs dithranol alone

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dithranol + BBUVB	Dithranol alone	Relative (95% CI)	Absolute	
Clear or nearly clear (≤1% BSA, ≤1 on all severity scores) (follow-up 8 weeks)											
1 Gerritsen 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	15/24 (62.5%)	7/24 (29.2%)	RR 2.14 (1.07 to 4.3)	333 more per 1000 (from 20 more to 963 more)	⊕⊕OO LOW
Irritation (requiring adjustment of dithranol) (follow-up 8 weeks)											
1 Gerritsen 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	2/24 (8.3%)	4/24 (16.7%)	RR 0.50 (0.1 to 2.48)	83 fewer per 1000 (from 150 fewer to 247 more)	⊕OOO VERY LOW
Median time to clear (follow-up 8 weeks; Better indicated by lower values)											
1 Gerritsen 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[d]	none	15	7	-	MD 0.7 lower Combi: 5.7 weeks Dithranol: 6.4 weeks	⊕⊕OO LOW

(a) No allocation concealment
(b) Confidence interval ranges from clinically important effect to no effect
(c) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect

(d) No measure of variance reported

9.5.8.2 Evidence statements

In people with psoriasis, dithranol (micanol) plus BBUVB was statistically significantly better than dithranol alone for:

- Clear or nearly clear (≤1% BSA, ≤1 on all severity scores) at 8 weeks [1 within-patient study, 24 participants (48 randomised units), low quality evidence][297]

In people with psoriasis, there was no statistically significant difference between dithranol (Micanol) plus BBUVB versus dithranol alone for:

- Irritation (requiring adjustment of dithranol) at 8 weeks [1 within-patient study, 24 participants (48 randomised units), very low quality evidence][297]

Evidence statements for individual studies where no statistical analysis could be performed comparing dithranol (micanol) plus BBUVB versus dithranol alone:

- The median number of weeks to achieve clear or nearly clear status was shorter with the combination regimen after a maximum follow-up of 8 weeks [1 within-patient study, 15 participants (22 randomised units), low quality evidence][297]

9.5.9 Dithranol (micanol) plus BBUVB vs placebo plus BBUVB

9.5.9.1 Evidence profile

Table 107: Evidence profile comparing dithranol (micanol) plus BBUVB vs placebo plus BBUVB

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dithranol + BBUVB	Placebo + BBUVB	Relative (95% CI)	Absolute	
Clear or nearly clear (≤1% BSA, ≤1 on all severity scores) (follow-up 8 weeks)											
1 Gerritsen	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	15/24 (62.5%)	11/24 (45.8%)	RR 1.36 (0.8 to 2.33)	165 more per 1000 (from 92 fewer to 610 more)	⊕⊕OO LOW

1998											
Median time to clear/nearly clear (follow-up 8 weeks; Better indicated by lower values)											
1 Gerritsen 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	15	11	-	MD 0 Combi: 6.4 weeks Dithranol: 6.4 weeks	⊕⊕OO LOW

(a) No allocation concealment
(b) Confidence interval ranges from clinically important effect to no effect
(c) No measure of variance reported

9.5.952 Evidence statements

In people with psoriasis, there was no statistically significant difference between dithranol (micanol) plus BBUVB versus placebo plus BBUVB for:

- Clear or nearly clear (≤1% BSA, ≤1 on all severity scores) at 8 weeks [1 study, 24 participants (48 randomised units), low quality evidence] [297]

Evidence statements for individual studies where no statistical analysis could be performed comparing dithranol (micanol) plus BBUVB versus placebo plus BBUVB:

- The median number of weeks to achieve clear or nearly clear status was the same with both treatments after a maximum follow-up of 8 weeks [1 within-patient study, 15 participants (26 randomised units), low quality evidence] [297]

9.5.953 Dithranol (short-contact) plus coal tar plus BBUVB vs dithranol

The short-contact dithranol intervention included salicylic acid in the formulation and is likely to have been administered in a day-care setting, unlike micanol, which is suitable for home use.

9.5.964 Evidence profile

Table 108: Evidence profile comparing dithranol (short contact) plus coal tar vs dithranol

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dithranol + Coal Tar + BBUVB	Dithranol	Relative (95% CI)	Absolute	
Clearance (follow-up 3 weeks)											
1 Paramsothy 1988	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	20/27 (74.1%)	16/26 (61.5%)	RR 1.2 (0.83 to 1.75)	123 more per 1000 (from 105 fewer to 462 more)	⊕OOO VERY LOW
Mean number of days to clearance (follow-up 3 weeks; Better indicated by lower values)											
1 Paramsothy 1988	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27	26	-	MD 0.8 higher (0.37 lower to 1.97 higher)	⊕⊕OO LOW
Mean number of weeks to relapse among clearers (follow-up unclear ; Better indicated by higher values)											
1 Paramsothy 1988	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	16	-	MD 8.3 higher Combination: 18.9 Dithranol alone: 10.6	⊕⊕OO LOW
Relapse rate (post-treatment) (follow-up unclear time post-treatment)											
1 Paramsothy 1988	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	14/20 (70%)	13/16 (81.3%)	RR 0.86 (0.59 to 1.25)	114 fewer per 1000 (from 333 fewer to 203 more)	⊕OOO VERY LOW

(a) Unclear method of randomisation, no allocation concealment, unblinded
(b) Confidence interval ranges from clinically important effect to no effect
(c) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect

9.5.9.5 Evidence statements

In people with psoriasis, there was no statistically significant difference between dithranol plus coal tar plus BBUVB versus dithranol for:

- Clearance at 3 weeks [1 between-patient study, 53 participants, very low quality evidence][298]
- Mean number of days to clearance after a maximum of 3 weeks [1 between-patient study, 53 participants, low quality evidence][298]
- Relapse rate post treatment [1 between-patient study, 36 participants, very low quality evidence][298]

Evidence statements for individual studies where no statistical analysis could be performed comparing SCDT plus coal tar plus BBUVB versus dithranol:

- Mean time to relapse among those who cleared was longer with SCDT + BBUVB + coal tar versus dithranol alone [1 between-patient study, 53 participants, low quality evidence][298]

9.5.10 Economic evidence

No relevant economic evidence was identified. Two studies were excluded due to poor applicability and/or serious methodological limitations. Hartman and colleagues[299] performed a cost-effectiveness analysis comparing short contact dithranol versus UVB phototherapy versus inpatient dithranol therapy; however, it did not compare any of these interventions in combination and thus it did not meet the inclusion criteria of the protocol and was excluded. One study [300] was excluded due to very serious methodological limitations.

9.5.10.1 Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs were sourced to aid consideration of cost effectiveness. In the case of dithranol and crude coal tar, costs are quite variable. Products listed in the BNF, are typically of lower concentrations and are intended for home use and application. Dithranol and crude coal tar products that are used in specialist day centres are of higher concentrations and are available as 'specials' from licensed 'special-order' manufacturers. Table 109 presents unit costs for the home use products included in the BNF and Table 110 presents unit costs of 'specials' from a selection of licensed NHS hospital manufacturing units.

Table 109: Costs of medications for home use

Item	Cost(a)	Notes
Dithranol		
Dithrocream® (Dermal)	0.1%, 50 g = £3.77; 0.25%, 50 g = £4.04; 0.5%, 50 g = £4.66; 1%, 50 g = £5.42; 2%, 50 g = £6.79. £15.08	Cream Dose for application to skin or scalp; 0.1–0.5% cream suitable for overnight treatment, 1–2% cream for max. 1 hour 200g per week of 0.1% (a)
Micanol ® (GP Pharma)	1%, 50 g = £13.48; 3%, 50 g = £16.79	Cream Dose for application to skin or scalp; 1% cream for up to 30 minutes once daily; 3% cream under medical supervision
Crude coal tar		
Coal Tar Solution, BP	net price 500 mL = £8.16.	Dose: 100mL dose in bath Based on 1 bath per day: Daily: £1.63 Weekly: £11.42 Note Strong Coal Tar Solution BP contains coal tar 40%
Carbo-Dome® (Sandoz)	net price 30 g = £4.77, 100 g = £16.38	Dose psoriasis, apply to skin 2–3 times daily Cream, coal tar solution 10%, in a water-miscible basis,
Exorex® (Forest)	5%, 100 mL = £8.11 5%, 250 mL = £16.24	Dose psoriasis, apply to skin or scalp 2-3 times daily

Item	Cost(a)	Notes
		Lotion, coal tar solution 5% in an emollient basis
Psoriderm® (Dermal)	6%, 225 mL = £9.42	Does psoriasis, apply to skin or scalp 1-2 times daily Cream, coal tar 6%, lecithin 0.4%
Vitamin D or vitamin D analogue		
Calcipotriol (Non-proprietary)	50 micrograms/g, net price 120 g = £24.04 50 micrograms/mL, net price 60 mL = £12.53, 120 mL = £26.07	Ointment, calcipotriol Scalp solution, calcipotriol
Dovonex® (LEO)	50 micrograms/g, net price 120 g = £22.66 50 micrograms/g, net price 120 g =£23.10	Cream, calcipotriol Ointment, calcipotriol
Silkis® (Galderma)	3 micrograms/g, net price 100g = £13.87	Ointment, calcitriol
Curatoderm® (Almirall)	4 micrograms/g, net price 30 mL = £12.73 4 micrograms/g, net price 30 g = £13.40, 60 g = £23.14, 100 g = £30.86	Lotion, tacalcitol (as monohydrate) Ointment, tacalcitol (as monohydrate)

(a) BNF 62, 2011[301]

(b) Dosage estimate based on mean quantities found in Hartman et al. 1998, who estimated for short contact treatment 62 Dithranol pots (0.1%-5.0%, 40 grams) were used daily over 12 weeks, equating to 207 grams per week. For inpatient treatment, they estimated 22 Dithranol pots (0.05%-5.0%, 40 grams) were used over a period of 8 weeks, equating to 110 grams per week.

Table 110: Costs of medications for specialist day centre use

Treatment	Strength	Dose and cost
Crude coal Tar		
Coal Tar, crude, in YSP Ointment	1%	Ointment 100g £22.90
Coal Tar, crude, in YSP Ointment	2%	Ointment 100g £22.90
Coal Tar, crude, in YSP Ointment	5%	Ointment 100g £23.00
Coal Tar, crude, in YSP Ointment	10%	Ointment 100g £23.20
Coal Tar, crude, in YSP Ointment	20%	Ointment 100g £23.50
Coal Tar, crude, in YSP Ointment	10%	Ointment 80g £10.99
Coal Tar Solution in ¼ Strength Betnovate		
Dithranol		
Dithranol in Lassar's Paste Ointment	0.25%	Ointment 100g £20.56
	0.50%	Ointment 100g £20.93
	1%	Ointment 100g £21.42
	2%	Ointment 100g £22.40
	4%	Ointment 100g £24.43
	6%	Ointment 100g £26.46

Treatment	Strength	Dose and cost
	10%	Ointment 100g £28.49
Dithranol Pomade Scalp cream	0.40%	Cream 100g £50.00
		Synalar gel Mix 100g £42.31

Source: All costs obtained through personal communication with Lead pharmacist of Dermatology and Allergy at Guy's & St Thomas' NHS Foundation Trust, 13 May 2011.

The unit costs for 'specials' are dependent on the ingredients, quantities, pack size and batch size, with the most significant drivers being concentration (due to ingredients) and batch size. Based on personal communications with pharmacy technicians and directors at a variety of NHS hospital manufacturing units (Calderdale & Huddersfield NHS Foundation Trust, Colchester Hospital University NHS Foundation Trust, Eastbourne Pharmaceuticals at Eastbourne District General Hospital, Guy's & St Thomas' NHS Foundation Trust, Royal Free Hospital), dithranol and crude coal tar produced in batches are quite modest in cost (between £5 and £22 per 100 g depending on concentration); however, when prepared extemporaneously (individually compounded products) the cost is significantly greater (£70 to £150 per 100 g depending on concentration). Several NHS hospital manufacturing units also indicated that they had either reduced preparation of these 'specials' or had stopped making them altogether due to low demand or increasing difficulty in sourcing suitable raw materials. Based on this information, it seems reasonable to conclude that outside of very busy specialty dermatology units, it is very likely that dithranol and crude coal tar 'specials' will be prepared extemporaneously and therefore have high unit costs.

Table 111: Unit cost of phototherapy and psoriasis-related day case hospital visit

Item	Cost	Notes
Phototherapy	£82	NHS Reference Costs 2009/10 for phototherapy (JC29Z) delivered in an outpatient setting
Photochemotherapy	£131	NHS Reference Costs 2009/10 for phototherapy (JC32Z) delivered in an outpatient setting
Daycase	£351	NHS Reference Cost 2009/10 for day case treatment of psoriasis (JD02C) without comorbidities or complications

Source: NHS Reference Costs 2009/10

9.5.10.2 Evidence statements

- No cost-effectiveness analyses were identified comparing narrowband UVB combined with dithranol, coal tar, or vitamin D or its analogues compared with narrowband UVB, dithranol, coal tar or vitamin D or vitamin D analogue alone.

9.6 Recommendations and link to evidence

Recommendations on phototherapy	**65. Consider topical adjunctive therapy in people receiving phototherapy with broadband or narrowband UVB who:** • **have plaques at sites that are resistant or show an inadequate response (for example, the lower leg) to phototherapy alone, or at difficult-to-treat or high-need, covered sites (for example, flexures and the scalp)** • **do not wish to take systemic drugs or in whom systemic drugs are contraindicated.**

Future research recommendations	**16. In people with psoriasis, when inducing remission, what are the clinical effectiveness (including duration of remission and psychological benefit), cost effectiveness, safety, tolerability and patient acceptability of complex topical therapies with or without NBUVB compared to a short course of systemic therapy (for example, ciclosporin)?**
Relative values of different outcomes	• The outcomes were not prioritised for considering imprecision, as so few of the outcomes required decisions about imprecision.
Trade off between clinical benefits and harms	The topical treatments are messy and inconvenient in terms of application and additional time, and minimal or no benefit was evident either in terms of reduced UV exposure or improved efficacy when used as adjunctive therapy with UVB so for the majority of patients adjunctive topical therapy is not be justified. See 'other considerations' sections for additional discussion risk/benefit trade off and special situations where topical therapy is indicated
Economic considerations	There was no economic evidence to inform the GDG on the comparative cost-effectiveness of combination strategies such as Goekerman's regimen (crude coal tar plus UVB), Ingram's regimen (dithranol plus UVB) or vitamin D or vitamin D analogue and UVB compared to any of their components alone. The clinical evidence suggested that there may be some additional benefit gained from combining these topicals with UVB compared to UVB alone or the topical alone, but the results are subject to substantial uncertainty. The clinical evidence also suggested that combination therapy with topicals and UVB may reduce either the time to clearance or the number of treatments to clearance or both; however, these results also varied across trials and do not allow for any firm conclusions to be drawn. In the absence of any formal economic analysis, the GDG considered the cost of the topicals themselves and the cost of the time and expertise needed for their effective application. Costs for these interventions vary substantially and involve a high degree of specialist supervision, and there is inconclusive evidence regarding the incremental benefit of such combinations. They could not be certain that these treatment strategies represented better value for NHS resources over other UVB therapy alone; therefore they chose not to recommend it routinely for all patients. Despite the limited and inconclusive evidence, the GDG believed there to be a role for these safe and historical mainstays of psoriasis treatment in the management of some patients. They believed that the addition of crude coal tar, dithranol or vitamin D or vitamin D analogue may provide additional benefits at a reasonable additional cost for patients whose psoriasis is concentrated sites that are difficult to treat with UVB therapy or topical alone. They also considered the use of these combination regimens likely to be cost-effective compared to continued UVB therapy or topicals alone among people not wishing or unable to be escalated to systemic non-biological or biological therapy.
Quality of evidence	• Overall there is a lack of consistency in the findings, with most

studies having serious or very serious limitations.

- Follow-up time in the studies is variable and often inappropriately short (not reflective of clinical practice; 4-6 weeks)
- Difficult to draw conclusions owing to the variable definitions of outcomes reported and the different intervention schedules employed
- There is also a lack of evidence for the important outcome of relapse and for safety data
- Adding UVB to topical therapy appears to provide clinical benefit compared with topical therapy alone which provides evidence to support the recommendation 'offer NBUVB phototherapy to people with chronic plaque or guttate pattern psoriasis that are inadequately controlled with topical treatments alone. Treatment with NBUVB phototherapy should be given two or three times weekly depending on patient preference. Patients should be aware that time to response may be shorter with three times weekly NBUVB' (see 9.2).

The key studies were those that compared UVB + topicals with UVB alone, to establish the added benefit of adjunctive topical therapy among those who require phototherapy:

- In the Ramsey study comparing BBUVB + vitamin D analogue vs. BBUVB alone the intervention group were given BBUVB twice weekly whereas the control group were given BBUVB three times weekly, making it difficult to comment on efficacy or UV-sparing effect as any difference could be due to treatment frequency rather than the adjunctive topical therapy; no clinically relevant difference was seen in the time to achieve remission.
- The studies addressing the value of NBUVB + vitamin D analogue vs. NBUVB alone show overall no benefit of adding vitamin D analogue as a UV sparing agent; some of the studies suggested there may be some benefit in terms of improved response rates but the quality of the evidence is was poor; these uncertain benefits needs to be balanced against the increased cost and inconvenience of topical therapy with vitamin D analogues. One study (Rim) demonstrated that the benefit of adding a topical vitamin D analogue was greater for the extremities than the trunk, which is in line with clinical experience that the lower legs often take longer to respond to UVB.
- BB UVB + concomitant therapy with vitamin D analogue does appear to reduce number of UV treatments (but these differences in terms of absolute number of UVB treatments) were not deemed to be clinically significant) and improve efficacy. It is possible that the difference in findings between NB and BBUVB reflect differences in efficacy between the two forms of UVB treatment (i.e. a greater increase in efficacy is seen with BBUVB when adding a vitamin D analogue because the baseline efficacy is lower, although please note the findings from chapter 9.1.2 where NBUVB and BBUVB were of similar efficacy). BBUVB is not widely used to treat psoriasis having been superseded by NBUVB.
- The studies of adjunctive tar or dithranol with UVB were too few and

	of insufficient quality to be confident about the value or otherwise of these therapies in conjunction with UVB therapy.
Other considerations	• Some ointment based topicals can block UV light and need to be applied after phototherapy. The GDG noted the lack of information about timing of ointment application in the studies. • The GDG recognised that some healthcare professionals may be using vitamin D or vitamin D analogues as an adjunct to UVB in the belief that it is safer for patients, and this is not supported by the evidence. However, the studies addressing this question were too short, and of insufficient quality to be confident that adjunctive therapy is not of value and therefore the GDG feel justified in making a recommendation. • UVB phototherapy is an effective and widely used treatment for psoriasis, but there is an outstanding question about the additional benefit of adjunctive topical therapy either self applied, or in a daycare, specialist setting. From clinical experience, the traditional Ingrams/Goekemans regime were cited as being effective and helpful in the management of psoriasis in people who did not wish to take or could not take systemic therapies. The GDG did not wish to make a future research recommendation as this was not considered to be a high priority area for research. • GDG experience, and to a degree, the limited evidence available, suggest that these complex topical interventions are effective and induce durable remission in an important proportion of patients. Some patients value the daily contact with specialist nurse expertise and social support provided in day care settings, and/or want to avoid or cannot use systemic therapy. • The GDG felt it would be helpful to delineate the specific groups in whom UVB with adjunctive therapy could be beneficial, including: o Those who are not making satisfactory progress on UVB alone o Those who do not wish to take systemic drugs, or in whom systemic drugs are contraindicated o Those with plaques at resistant sites, for example the lower leg, or at sites not exposed to UVB, for example the scalp, flexures and genitals. • The value of additional NBUVB is unclear. Dithranol /crude coal tar with or without NBUVB is widely used in dermatology practice but is expensive to deliver. The place of these interventions in the context of modern practice is unclear, nor is the value of co-therapy with NBUVB. The GDG agreed that evaluating the clinical effectiveness, cost effectiveness and tolerability of dithranol/crude coal tar in day care / inpatient settings compared to NBUVB alone and compared to short term systemic therapy (for example, ciclosporin) would be justified.

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9.7 Phototherapy, systemic therapy (biological and non-biological), tar and risk of skin cancer

9.7.1 Clinical introduction

Skin cancers are very common in the general population. They constitute the most common group of cancers in the UK with approximately 60,000 new cases registered in England and Wales each year, accounting for 20% of all cancer registrations. There are many types of skin cancer, but three types are responsible for more than 95% of all skin cancers. These are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM). BCC and SCC are often grouped together as non-melanoma skin cancer (NMSC). MM, although far less common (around 10% of skin cancers) than NMSC, is the major cause of death from skin cancer, but overall the risk of death associated with majority of skin cancers is low, and most are completely cured with local, predominantly surgical, measures. Epidemiological studies clearly identify overexposure to sunlight in people with sensitive skin types as the main risk factor for skin cancer.

Tar, broadband UVB from fluorescent and other light sources have been available as a psoriasis therapy for the majority of the last century. Early concern that they may be associated with an increase in skin cancer incidence did not lead to careful study. It was murine work following the advent of PUVA in the 1970's that predicted a skin cancer problem in high usage patients. Clinical studies in North America and Europe followed over the next decade. After the introduction of narrowband UVB (NBUVB) therapy, initially into Europe in the 1980's and subsequently a decade later in North America, skin cancer risk was investigated.

Data from the organ transplant population indicate that long term immunosuppression carries an increased risk of NMSC, mostly attributable to an increased incidence of SCC and these findings may also be relevant to people with psoriasis treated with drugs that affect the immune system such as ciclosporin (CSA), methotrexate (MTX) or biological drugs.

Psoriasis is a chronic condition, and for many people involves protracted, sometimes life long, treatment. Multiple interventions may be used in a single individual at various times over the life time of their disease, and include some or all of the various treatment modalities available. In planning treatment it is clearly important to consider the efficacy of any treatment, or combination of treatment, against potential risks, which in the case of skin cancer, may take many years to manifest, and be modified by both past and future treatments. While it's recognised that some individuals will be more susceptible than others for a variety of reasons including skin type (see Fitzpatrick classification system in the Glossary), clinicians and their patients need a clear understanding of the skin cancer risks of therapy. This question therefore seeks to establish the size of skin cancer risk associated with the various treatment modalities, highlight aspects of treatment use such as duration of phototherapy that allow risk (s) to be minimised, and identify groups of people who either because of historical or current therapeutic practice, may be at especially high risk and therefore require active skin cancer surveillance.

The GDG agreed to pose the following question: in people with psoriasis who have been exposed to coal tar, phototherapy (BBUVB, NBUVB and PUVA), systemic therapy (biological or non-biological) therapy, what is the risk of skin cancer and which individuals are at particular risk?

9.7.12 Methodological introduction

9.7.2.1 Review protocol

A literature search was conducted for RCTs, prospective cohort studies or systematic reviews that addressed whether the risk of skin cancer is increased in people with psoriasis and whether there are subgroups of the psoriatic population who are at particularly high risk.

No time limit was placed on the literature search. The sample size was required to be sufficient to result in at least 10 cancer cases per covariate and studies were restricted to those with an average of at least 12 months follow-up since first treatment. Indirect populations were excluded but retrospective studies were included if no prospective data were available for a particular intervention that may be a risk factor for cancer.

The outcomes considered were:

- Melanoma
- Non melanoma skin cancer
    - Stratified in to squamous cell carcinoma and basal cell carcinoma if data were available

Subgroup analysis was considered for the following prognostic factors (in addition to the stated interventions that were considered to be potential risk factors):

- Skin type
- Concomitant or previous immunosuppressive treatments
- Duration of previous systemic treatment
- Cumulative exposure to previous systemic treatment or coal tar
- Previous exposure to ionising radiation
- Disease severity
- Previous skin cancer
- Age at first exposure
- Smoking
- Alcohol consumption
- Family history of skin cancer

Any interactions between the prognostic factors indicating whether there was additive risk were also extracted.

9.7.2.2 Included studies

Nineteen studies[302-320] were found that addressed the question and were included in the review.

- No suitable RCT data were available owing to the limited duration of follow-up and insufficient sample sizes
- The majority of the studies reported on the same cohort followed-up at different time points[303,305-307,309-318]
- Two studies[319,320] addressed the risk of skin cancers in people with psoriasis treated with biological therapies.
- One study[308] compared the incidence of skin cancer in people with psoriasis treated with systemic treatments or coal tar and people with psoriasis not treated with these interventions. This

allowed attribution of the increased risk to the interventions rather than any intrinsic risk associated with the psoriasis itself. The comparison of the incidence in a treated psoriasis cohort compared with a matched general population was also considered to be applicable. This provided indirect evidence from which inference can be made about the risk in people with psoriasis treated with systemic/phototherapy. However, the full treatment history remains unclear (and uncontrolled for). Because of this any difference in risk compared with the general population to the particular intervention being studied is difficult to determine. Note also that this comparison leads to risk of bias as the exposed and unexposed cohorts are selected from different sampling frames.

- No data (prospective or retrospective) were available for the biologics with follow-up of > 12 months.
- No data were available for the risk in children.

A summary of the characteristics of included studies is given in Table 112. Note that the number of patients given is the number of people in the psoriasis cohort, which was compared in the studies with the incidence rate of skin cancer among a matched general population sample (sample size not specified).

Table 112: Summary of characteristics of included studies

Reference	Number of patients	Patient group	Location	Mean follow-up period (years)	Outcomes	Notes
STERN1979	1380	PUVA cohort[a]	USA[b]	2.1	Non-melanoma skin cancer • Person counts[c] (unclear)	Reported all histologically confirmed non-melanoma skin cancers (unclear if pre-malignant forms included) PUVA regimen for all PUVA cohort studies: 0.4–0.6 mg/kg psoralen orally, followed in 1.5–2.0 h by UVA Initial UVA dose 1.5–5 J/cm^2 depending on photosensitivity. Two or three light treatments per week and UVA dose is gradually increased as tolerated. With disease improvement therapy slowly tapered off. If disease flared, patients treated again with PUVA or other therapies for psoriasis as determined by their physician.
STERN1984	1380	PUVA cohort[a]	USA[b]	5.7	Non-melanoma skin cancer	Reported all histologically confirmed non-melanoma skin cancers (unclear if pre-malignant forms included)
STERN1984A	1380	PUVA cohort[a]	USA[b]	5.7	SCC and BCC • Person counts[c] • Population rates[d]	Only included incident tumours occurring 22 months after initial PUVA treatment Excluded SCC *in situ* and keratoacanthoma (although observed incidence is recorded)
STERN1988A	1380	PUVA cohort[a]	USA[b]	>10	SCC and BCC • Person counts[c] • Population rates[d]	Reported all histologically confirmed non-melanoma skin cancers (unclear if pre-malignant forms included) Only included incident tumours occurring 58 months after initial PUVA treatment • first incident tumour after at least 58 months • any incident tumour after at least 58 months (even if the patient had a first tumour prior to this)
STERN1990	892	PUVA cohort[a]	USA[b]	12.3	Genital SCC	Included invasive and *in situ* tumours

Reference	Number of patients	Patient group	Location	Mean follow-up period (years)	Outcomes	Notes
		– male subgroup			• Tumour counting unclear (appears to be total count)	
STERN1994	1380	PUVA cohort[a]	USA[b]	13.2	SCC and BCC • Person counts[c] • Population rates[d]	Excluded SCC *in situ*
STERN1997	1380	PUVA cohort[a]	USA[b]	20.2	Malignant melanoma • Population rates	Included invasive melanoma only
STERN1998A	1380	PUVA cohort[a]	USA[b]	20	SCC and BCC • Person counts[c] • Population rates[d]	Excluded SCC *in situ* Separately assessed those with tumour development during the first decade and those surviving without tumour occurrence by the end of the first decade – to assess increasing risk as time since first treatment increases
STERN2001	1380	PUVA cohort[a]	USA[b]	22.4	Malignant melanoma • Population rates	Stratified for invasive and *in situ* melanoma
STERN2002	892	PUVA cohort[a] – male subgroup	USA[b]	>20	Genital SCC • Person counts[c] • Population rates[d]	Included invasive and *in situ* tumours
MARCIL2001	1380	PUVA cohort[a]	USA[b]	6 years for CSA (20 years for PUVA)	SCC and BCC • Tumour counting unclear (appears to be total count)	Included pre-malignant lesions (keratoacanthoma and SCC *in situ* – Bowen's disease) Note: approximately 86% of all SCCs were invasive
NIJSTEN2003	135	PUVA cohort[a] – retinoid treated subgroup	USA[b]	≥1 year for retinoids (mean = 4 years)	BCC and SCC • Total tumour count (population rate calculated for	Included pre-malignant lesions (keratoacanthoma and SCC *in situ* – Bowen's disease)

Reference	Number of patients	Patient group	Location	Mean follow-up period (years)	Outcomes	Notes
					sensitivity analysis found no difference)	
NIJSTEN2003A	1380	PUVA cohort[(a)]	USA[(b)]	>20	BCC and invasive SCC • Total tumour count	Included only biopsy confirmed SCC, not SCC *in situ* or keratacanthoma
LIM2005	1380	PUVA cohort[(a)]	USA[(b)]	28 (>15 years for UVB)	BCC and invasive SCC • Population rates (i.e., incident tumours)[(d)] • Total tumours	Excluded keratacanthoma and SCC *in situ*
PAUL2003	1252	CSA cohort	International (Europe and N. America)[(d)]	Median 4.5 years	BCC, SCC and melanoma • Tumour counting unclear	Included only malignant forms Mean starting dose 3 mg/kg/d; mean daily dose decreased over time from 3.1 mg/kg/d at month 6 to 2.7 mg/kg/d at the end of month 54. Approximately 40% of all patients received CSA intermittently and the remaining 60% received it continuously.
PAPP2012A	506	Etanercept cohort	Canada	Up to 4 years	Non-melanoma skin cancer • Total counts	General population reference data were only available from USA registries, so the exposed and unexposed cohorts were not match on geographic location, which will effect sun exposure and skin cancer rates. This confounding variable was not accounted for in the analysis
VANLUMIG2012	173	Biologics cohort	The Netherlands	5 years	BCC and SCC • Total counts	Biologics included etanercept, adalimumab, infliximab, ustekinumab, efalizumab, alefacept and onercept – note alefacept and onercept were only used pre-enrolment to the registry. Dose and interval changes were according to the opinion of the dermatologist and topical or systemic therapies could be added as required. Prior treatment and medical history was not controlled for and the short time to onset for many events suggests that the biological agent may not

Reference	Number of patients	Patient group	Location	Mean follow-up period (years)	Outcomes	Notes
						have influenced the pathogenesis
HEARNE2008 (MAN2005)	2130	NBUVB cohort	UK - Scotland	Median: 5.5 years	BCC, SCC and melanoma • Person counts[(c)]	Included cases classified as skin cancer by ICD (9th or 10th revision) codes All results taken from 2008 study as too few cases in 2005 preliminary report

SCC: Squamous cell carcinoma
BCC: Basal cell carcinoma
(a) These publications all relate to the same cohort followed over time
(b) The standard PUVA regimen during the early years of its use differed between the USA and Europe (in Europe the tendency was to use 3 courses of PUVA and to minimise the total number of joules, whereas the US model used a higher number of treatments and continuous treatment rather than defined courses). This study collated data from 16 centres across the USA.
(c) Person counts: if a tumour of a given type developed, that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours occurred – this would give a lower incidence than the federal survey data, which was used to calculate expected values used as a comparator group, and so the excess risk associated with PUVA may be underestimated. This is a conservative estimate)
(d) Population rates: annual incidence by counting only the first tumour of a given type observed that year, but continuing individuals in the risk set after tumour occurrence (this is in line with the federal survey data used for expected values).
(e) Includes Austria, Canada, Denmark, France, Germany, Great Britain, Italy, Portugal, Spain, Switzerland and Turkey

Due to the design of the studies considered, GRADE could not be used to assess quality. Quality was assessed using a modified version of the Checklist for Prognostic Studies[29] (see Table 113). The quality rating was derived by assessing the risk of bias across 5 domains (selection bias; attrition bias; prognostic factor bias; outcome bias; and confounders and analysis bias) and although listed per study the adequacy of outcome measurement and controlling for confounders were considered per outcome; however, the rating was the same across outcomes unless otherwise stated.

For all studies the unexposed cohort was a general population sample and so would have included a proportion with psoriasis and potentially with exposure to the interventions beings assessed as risk factors (e.g., PUVA or ciclosporin). Also, in the Stern cohort 39 patients had a history of skin cancer before PUVA and this was not controlled for in all analyses. Across all studies there was high risk for outcome surveillance bias as there is likely to be more complete ascertainment of skin cancer cases among the exposed cohort who were actively followed-up and examined compared with the general population where diagnoses may be missed. None of the studies reported how missing data were handled or if imputation was used.

Table 113: Study quality checklist

Reference	Quality assessment – study methodology

Reference	Quality assessment – study methodology							
	Prospective	Representative population sample[a]	Minimal attrition bias	Prognostic factor measured appropriately[b]	Outcomes adequately measured	Confounders accounted for[c]	Appropriate statistical analysis[d]	Quality
STERN1979	✓	✓	✓	✓	✓	~	×[e]	LOW
STERN1984	✓	✓	✓	✓	✓	×	×[e]	VERY LOW
STERN1984A	✓	✓	✓	✓	✓	~	✓ - for subgroup comparisons × - for general population comparison	Subgroups: MODERATE Main: LOW
STERN1988A	✓	✓	?[f]	✓[g]	✓	~	×[e]	LOW
STERN1990	✓	✓	?[f]	✓	✓	~	×[e]	LOW
STERN1994	✓	✓	?[f]	✓	✓	~	✓ - for subgroup comparisons × - for general population comparison	Subgroups: MODERATE Main: LOW
STERN1997	✓	✓	?[f]	✓[g]	✓	~	×[e]	VERY LOW
STERN1998A	✓	✓	?[f]	✓[g]	✓	~	✓- for subgroup comparisons × - for general population comparison	Subgroups: MODERATE Main: LOW
STERN2001	✓	✓	?[f]	✓[g]	✓	~	✓ (but too few events)	VERY LOW

Reference	Quality assessment – study methodology							
STERN2002	✓	✓	?[f]	✓	✓	~	✓ - for PUVA dose comparisons (but too few events) × - for main analysis	VERY LOW
MARCIL2001	✓	✓	?[f]	✓	✓	~	✓	LOW
NIJSTEN2003	✓	×[h]	?[f]	✓	✓	~	✓ (but too few events)	LOW
NIJSTEN2003A	✓	✓	?[f]	✓	✓	~	✓	MODERATE
LIM2005	✓	✓	?[f]	✓	✓	~	✓	MODERATE
PAUL2003	✓	✓	×	✓	✓	~	✓ (but too few events)	VERY LOW
PAPP2012A	×/✓[i]	✓	×	✓	?	×	×[e]	VERY LOW
VANLUMIG2012	✓	✓	?	?	✓	×	×[e]	VERY LOW
HEARNE2008 (MAN2005)	×	✓	?[j]	✓	✓	×	×[e]	VERY LOW

×: No
✓: Yes
~ : Partial
?: Unclear
(a) The representativeness of the sample is based on baseline characteristics, although inclusion and exclusion criteria were not clearly stated. Although there are more skin types III+ than in the UK the geographical area also has a higher UV exposure than the UK and the exposed and unexposed samples were matched for geographic location so the sample is deemed appropriate

(b) Limited reliance on recall
(c) See Table 114 for detailed information on controlling for confounders
(d) Note that the method of calculating RR for subgroups differed (i.e., some used the relative SMR, the risk compared with the general population in each group, and some used an IRR directly comparing the incident rate in two groups; see Table 115)
(e) No multivariate regression analysis
(f) In the Stern cohort, after 1984 the numbers remaining in the follow-up assessments were <80%. However, the majority of this attrition was due to death at rate consistent with that expected in the general population. Withdrawal and loss-to-follow-up for reasons other than death was at an acceptable level considering the long-term nature of the study (<20% lost by 2001, 25 years after recruitment). However, the reasons for loss to follow-up were unclear and it cannot be determined whether the characteristics of those who withdrew from the study or were lost to follow-up were different from those who remained and could have skewed the results.
(g) It is unclear whether the threshold for stratification in PUVA dose subgroup analyses was pre-specified or chosen based on the data, which could lead to bias
(h) Those who received retinoids and were included in this study had higher PUVA exposure among than the average for the full cohort
(i) This study has prospective and retrospective elements to its design
(j) All eligible individuals were included in the study but some data were missing and so were imputed

9.7.253 Confounding variables

In observational studies it is necessary to control or adjust for confounding variables, other than the stated intervention, that may also vary between the comparison groups and cause any observed differences. Therefore, in assessing study quality the adequacy of controlling for confounders was assessed.

Table 114 summarises which of the key confounders have been controlled for and by what method in each of the included studies. This information does not relate to the comparison of the risk of skin cancer in people with psoriasis versus the general population, which in all cases was based on an age-matched and sex- matched analysis, without controlling for other key confounders. The Stern cohort also matched for geographic location. The Hearne, Papp and van Lumig papers are excluded from Table 114 as they only provided data comparing observed rates with those expected in a matched general population sample.

Table 114: Adequacy of controlling for key confounders

Study	Confounder										Ratio of covariates to incidence >10
	Age	Sex	Geographic residence	Skin type	Immunosuppressive therapy (e.g., x-ray)	MTX use	CSA use*	PUVA	UVB	History of skin malignancy	
STERN1979	✓ [d]	✓ [d]	✓ [d]	✓ [e†]	✓ [e†]	×	-	×	×	✓ [e†]	N/A
STERN1984	×	×	×	✓ [e†]	×	×	-	×	×	×	N/A
STERN1984A	✓ [c]	✓ [c]	✓ [c]	×	✓ [d†]	×	-	✓ [e†]	✓ [d†]	×	✓
STERN1988A	✓ [c]	✓ [c]	×	✓ [e†]	✓ [b1†]	×	-	✓ [b1/e†]	×	×	N/A

Study	Confounder										Ratio of
STERN1990	✓ a	✓ a	×	×	✓ b2	✓ b2	-	✓ b2	×	×	N/A
STERN1994	✓ c	✓ c	✓ c	×	✓ d†	✓ d†	-	✓ e	✓ d†	×	✓
STERN1997	✓ c	✓ c	✓ c	×	×	×	-	✓ e	×	×	N/A
STERN1998A	✓ d	✓ d	✓ d	×	✓ d	✓ d	×	✓ d	×	×	✓
STERN2001	✓ d	✓ d	?	?	?	?	?	✓ d**	×	?	×
STERN2002	✓ c/d	✓ a	×	✓ b1	×	×	×	✓ d**†	×	×	×
MARCIL2001	✓ d	×	×	×	×	✓ d	✓ a	✓ d**	×	×	✓
NIJSTEN2003	✓ d	✓ d	×	×	✓ d	✓ d	×	✓ d**	×	✓ d	×
NIJSTEN2003A	✓ d	✓ d	✓ d	✓ d	✓ d	✓ d	×	✓ d**	✓ d	×	✓
LIM2005	✓ d	✓ d	✓ d	✓ d	×	✓ d	✓ d	✓ d**	✓ d	×	✓
PAUL2003	✓ c	✓ c	✓ c	×	✓ d	✓ d	✓ d	✓ d	×	✓ d	×

× *Uncontrolled for*
✓ *Controlled for*
? *Unclear if controlled for – study states adjusted for 'all other risk factors'*
N/A No multi-variable regression analysis
(a) Restricted participant selection so that all groups had the same value for the confounder (e.g. restricting the study to male participants only)
(b1) Demonstrated balance between subgroups for the confounder
(b2) Demonstrated balance between groups (cases and controls) for the confounder
(c) Matched on the confounder
(d) Adjusted for the confounder in statistical analyses to quantify the effect size
(e) Stratified for this variable
* *CSA was not licensed for use in severe psoriasis by the FDA in the USA until 1997*
† *This factor was not accounted for in all analyses*

** *Adjusted for PUVA dose/level of exposure only (i.e., not for any exposure to PUVA*

Pooling the results of observational studies is inappropriate owing to inconsistencies in design, comparison and potential confounders. All observational study data have been considered individually.

9.7.254 Summary statistics

A range of summary statistics are reported, some of which are specific to prognostic investigations. To aid interpretation, a summary of the definitions of these statistics is provided in Table 115. Estimates of the absolute risk are provided in Appendix Q.

Table 115: Defining summary statistics

Summary statistic	Definition
Incidence rate	Incident cases divided by the number in the cohort multiplied by the exposure time
Standardised incidence (SIR)/rate ratio (SRR)/ Standardised morbidity ratio (SMR)	Incidence rate observed among exposed divided by the incidence rate expected in a matched population
Relative standardised incidence/rate ratio Relative standardised morbidity ratio	Ratio between two standardized rate ratios (takes into account the difference in excess risk vs matched general population between two subgroups)
Incidence rate ratio (IRR)	Incidence rate among exposed divided by the incidence rate among non-exposed (direct comparison of risk between two subgroups)

9.7.3 PUVA

9.7.3.1 Risk vs. no PUVA exposure

One study[308], primarily designed to assess the risk associated with ciclosporin use, also assessed the independent risk for any skin carcinoma associated with PUVA exposure compared with those who had no exposure to PUVA. Skin carcinoma included squamous cell carcinoma (SCC), basal cell carcinoma (BCC) or any skin malignancy (SCC, BCC or malignant melanoma (MM). In total, 47% of the cohort had received some treatment with PUVA (Table 116).

9.7.3.2 Evidence summary

All skin cancer

Table 116: Relative risk of skin cancer in PUVA patients compared with non-PUVA-treated patients

Study	Relative risk*	
	Any skin malignancy	Any non-melanoma skin malignancy
PAUL2003	5.8 (2.0–25.0)	7.3 (1.3–134.5)

**From multivariate analysis using standardised incidence ratio (observed/expected) as outcome variable*

9.7.3.3 Evidence statements

- In people with psoriasis, the risk of non-melanoma skin cancer and of any skin cancer were statistically significantly higher among those treated with any level of PUVA compared with no PUVA treatment [1 study[308]; 1252 participants – 588 treated with PUVA; low quality evidence].

9.7.4 Risk vs. general population

Studies from the PUVA follow-up cohort provided information on the relative risk of skin cancer among people with psoriasis who have been, or are currently being, treated with PUVA compared with an age-, sex- and geographic location-matched general population sample based on incidence data. The data were stratified into squamous cell carcinoma, basal cell carcinoma and malignant melanoma.

9.7.4.1 Evidence summary

All non-melanoma skin cancer

One study[309] reported the overall relative risk of non-melanoma skin cancer in the PUVA cohort compared with the matched population. Based on a method that only counted the first tumour of each type per person (effectively measuring time-to-first tumour), the observed incidence in the psoriasis cohort was 2.63-times that expected in the matched age-, sex- and geographic location-matched general population (Table 117).

Table 117: Relative risk of non-melanoma skin cancer in PUVA patients compared with the general population

	Standardised morbidity ratio*
Study	Person counts
STERN1979	2.63 (1.91–3.90)

*Standardised morbidity ratio = numbers observed/numbers expected

Squamous cell carcinoma

Six studies[311-314,316,318] reported the relative risk of squamous cell carcinoma in the PUVA cohort compared with the matched population (Table 118).

When recording the annual incidence, by counting the first tumour of a given type observed that year, the observed incidence in the psoriasis cohort was 16.2-times that expected in 1984[311] and 27.0-times times that expected in 1994[314]. The earlier study (1984) only recorded tumours occurring at least 22 months after first treatment, whereas the later study (1994) appeared to include tumours from all time-points after treatment. Both only included invasive tumours.

Based on a method that only counted the first tumour of each type per person (effectively measuring time-to-first tumour), the observed incidence in the psoriasis cohort was 9.3-times that expected in 1984[311], 9.5-times in 1988[312] and 11.9-times in 1994[314] (Table 118). Additionally, calculation of the observed incidence starting from 10 years after first PUVA use demonstrated that the increased risk of developing SCC among PUVA-treated psoriasis patients persisted many years after PUVA treatment had been stopped in the majority of the cohort, with the relative risk being 17.6-times that expected in the period 1985-1998[316].

Two of these six studies specifically reported the incidence of genital tumours in men treated with PUVA (Table 118). In the 1990 report[313], based on the total number of tumours observed, the incidence of invasive genital SCC in the psoriasis cohort was 95.7-times that expected.

In the second report in 2002[318], when counting just the first tumour per person, the observed incidence of invasive genital SCC in the psoriasis cohort was 81.7-times that expected. The increased incidence again persisted after 1989 (the last date of surveillance for the 1990 report) at a level of 52.6-times that expected although use of PUVA had decreased and genital shielding in the cohort had increased. Similarly, the annual incidence of genital SCC observed in the psoriasis cohort in this study was 134.6-times that expected, and the increased incidence again persisted after 1989 at a level of 87.7-times that expected.

Table 118: Relative risk of SCC in PUVA patients compared with the general population

	Standardised morbidity ratio	
Study	**Population rates**	**Person counts**
STERN1984A	**All incident tumours after ≥22 months** 16.2 (13.0–19.9)	**All incident tumours after ≥22 months** 9.3 (6.9–12.2)
STERN1988A		**First tumour after ≥58 months** 9.5 (7.2–12.3) **All incident tumours after ≥58 months** 11.4 (9.1–14.2)
STERN1994	27.0 (24.2–30.1)	11.9 (10.1–14.0)
STERN1998A		**First cancer after 1985**[(a)] 17.6 (15.6–19.8)
Genital tumours		
STERN1990	Total count Invasive: 95.7 (43.8–181.8)	

Study	Standardised morbidity ratio	
	Population rates	Person counts
STERN2002	**After May 1989**[(b)] Invasive: 87.7 (42.1–161.3) Invasive + in situ: 89.4 (51.1–145.2) **Total follow-up** Invasive: 134.6 (89.5–194.6)	**After May 1989**[(b)] Invasive: 52.6 (19.3–114.6) Invasive + in situ: 61.5 (30.7–110.0) **Total follow-up** Invasive: 81.7 (52.1–122.6)

(a) The rate after 1985 was an arbitrary time-point chosen to investigate whether the risk changed at longer follow-up points

(b) The rate after 1989 was reported to capture the incidence since the last date of surveillance for the 1990 report

Basal cell carcinoma

Four studies[311,312,314,316] reported the relative risk of basal cell carcinoma in the PUVA cohort compared with the matched population (Table 119).

When recording the annual incidence, by counting the first tumour of a given type observed that year, the observed incidence in the psoriasis cohort was 2.2-times that expected in 1984[311] and 4.1-times times that expected in 1994[314]. The earlier study (1984) only recorded tumours occurring at least 22 months after first treatment, whereas the later study (1994) appeared to include tumours from all time-points after treatment. Both only included invasive tumours.

Based on a method that only counted the first tumour of each type per person (effectively measuring time-to-first tumour), the observed incidence in the psoriasis cohort was 1.7-times that expected in 1984[311], 2.3-times in 1988[312] and 2.5-times in 1994[314] (Table 119). Additionally, calculation of the observed incidence from 10 years after first PUVA use demonstrated that the increased risk of developing BCC among PUVA-treated psoriasis patients persisted (and even increased) many years after PUVA treatment had been stopped in the majority of the cohort, with the relative risk of first BCC after 1985 being 4.1-times that expected in the period[316].

Table 119: Relative risk of BCC in PUVA patients compared with the general population

Study	Standardised morbidity ratio	
	Population rates	Person counts
STERN1984A	**All incident tumours after ≥22 months** 2.2 (1.6–2.9)	**All incident tumours after ≥22 months** 1.7 (1.2–2.3)
STERN1988A		**First tumour after ≥58 months** 2.3 (1.8–2.9) **All incident tumours after ≥58 months** 2.1 (1.6–2.7)
STERN1994	4.1 (3.5–4.7)	2.5 (2.1–3.0)
STERN1998A		**First cancer after 1985**[(a)] 4.1 (3.7–4.6)

(a) The rate after 1985 was an arbitrary time-point chosen to investigate whether the risk changed at longer follow-up points

Malignant melanoma

One study[315] reported the overall risk of malignant melanoma in the PUVA cohort compared with the matched population. The observed annual incidence in the psoriasis cohort was 2.3-times that

expected in the matched age-, sex- and geographic location-matched general population over the full follow-up period. A breakdown of the incidence into an early and a late follow-up period demonstrated that the incidence in the PUVA cohort increased after 1990 (Table 120).

Table 120: Relative risk of MM in PUVA patients compared with the general population

	Standardised morbidity ratio (population rates)		
Study	1975–1990[(a)]	1991–1996[(a)]	1975–1996
STERN1997	1.1 (0.3–2.9)	5.4 (2.2–11.1)	2.3 (1.1–4.1)

(a) This stratification by date of follow-up was chosen because an apparent increase in rate of melanoma was noted beginning in 1991 (approximately 15 years after first PUVA treatment)

9.7.4.2 Evidence statements

In people with psoriasis treated with PUVA:

- The incidence of cutaneous cancer was statistically significantly increased compared with that expected in an age-, sex- and location-matched general population [7 studies[311-316,318]; 1380 participants; very low to low quality evidence]
- This increase was largely due to a higher rate of SCC [6 studies[311-314,316,318]; 1380 participants; very low to low quality evidence], with the ratio of observed-to-expected events being lower than that for SCC for both BCC [4 studies[311,312,314,316]; 1380 participants; very low to moderate quality evidence]and MM [1 study][315]; 1380 participants; very low quality evidence]
- There was a particularly increased incidence of genital SCC among men compared to the expected rates [2 studies[313,318]; 892 participants; very low to low quality evidence]
- The increased incidence of SCC persisted many years after cessation of PUVA [1 study[316]; 1380 participants; low quality evidence], and the incidence of BCC [1 study[316]; 1380 participants] and MM [1 study[315]; 1380 participants; very low quality evidence] appeared to increase at later time points

9.7.5 Risk modification factors

Some studies from the PUVA follow-up cohort also gave information on additional prognostic factors that could modify the risk of skin cancer associated with PUVA treatment in people with psoriasis.

9.7.5.1 Evidence summary

A1. PUVA dose (stratified dose subgroups compared with lowest dose subgroup as reference strata)

Nine studies[303,305,307,311,314-318] provided data (adjusted for at least age, sex and some relevant prior treatment exposure) regarding the relative risk of skin cancer in the PUVA treated cohort at various dose/exposure levels of PUVA compared with a reference strata, which was the lowest dose group, assumed to carry the lowest risk for skin cancer (see Appendix Q for definitions of high and low dose). A dose-risk relationship may suggest that PUVA can act as an independent carcinogen.

However, the statistics used to calculate the size of the effect varied (relative SMR[311,314,315,317], incidence rate ratio[303,305,307,318], odds ratio[316] or hazard ratio[307]), making direct comparison between the studies difficult.

Squamous cell carcinoma

Seven studies[303,305,307,311,314,316,318] provided data for the relative risk of SCC at different doses/levels of exposure to PUVA. Despite the different methods of analysis used, all of these studies showed a dose-response relationship, with increasing dose/levels of exposure showing incremental rises in the relative risk of skin cancer compared with the reference strata (Table 121).

Based on a method that only counted the first tumour of each type per person, compared with the low dose reference group the observed incidence was 5.7-times[311] or 2.6-times[314] higher in the medium dose group and 12.8-times[311] or 5.9-times[314] higher in the high dose group based on an adjusted standard morbidity ratio, which is linked to the ratio of observed-to-expected incidence. The reason for the reduction in risk between the time of the first and second studies is unclear, although only the later study[314] adjusted for MTX exposure.

When comparing multiple dose strata the relative risk or the time-to-first tumour (based on a hazard ratio) clearly increased with increasing numbers of exposures, whether using person counts, population rates or total tumour counts[303,305,307,316].

One study[316] showed that the odds of first cancer at least 10 years after first PUVA use increased with increasing cumulative exposure to PUVA during those 10 years (before 1985), while the levels of more recent PUVA exposure had a modest impact on tumour risk.

The risk of genital tumours was also increased at high compared with low PUVA dose, but this effect size was less pronounced than total SCC[318].

Table 121: Adjusted relative risk estimates for SCC at different levels of exposure to PUVA

	Multivariate adjusted risk estimate	
Reference	**Population rates**	**Person counts**
STERN1984A	-	**Relative SMR (incident tumours after ≥22 months)** Medium:low[(a)] 5.7 (2.4–13.9) High:low[(a)] 12.8 (5.8–28.5) *Note: if first SCC was detected after high PUVA dose, patients had a significantly higher mean number of tumours than those who developed SCC at low PUVA dose (3.4 vs 1.5; p <0.05)*
STERN1994	-	**RR (relative SMR)** Medium:low[(a)] 2.6 (2.0–3.3) High:low[(a)] 5.9 (4.0–8.7)
STERN1998A	-	**OR for first cancer after 1985[(b)]** *Total PUVA exposures to 1985* <100 1 100–159 1.6 (0.9–3.1) 160–336 4.5 (2.7–7.4) ≥337 8.6 (4.9–15.2) *PUVA exposures after 1985* ≥50 vs <50 1.4 (1.0–2.0)
MARCIL2001 (full cohort)	**IRR (tumour count unclear)** *PUVA exposures to 1992 or first CSA use[(c)]* < 200 1 ≥ 200 2.8 (2.6–3.2)	
NIJSTEN2003A	**IRR (all tumours counted)**	**HR (time to first tumour)**

Reference	Multivariate adjusted risk estimate			
	PUVA exposures		*PUVA exposures*	
	< 100	1	<100	1
	100–199	3.20 (2.27–4.51)	100–199	2.38 (1.60–3.54)
	200–299	5.28 (3.38–8.25)	200–399	6.03 (4.09–8.88)
	300–399	8.18 (4.95–13.53)	≥400	10.75 (6.99–16.54)
	400–499	14.36 (7.97–25.87)		
	≥500	18.67 (10.23–34.07)		
LIM2005	**IRR**		-	
	PUVA exposures			
	<100	1		
	100–199	2.36 (1.51–3.68)		
	200–299	4.14 (2.64–6.50)		
	300–399	5.54 (3.38–9.09)		
	400–499	11.05 (6.88–17.76)		
	≥500	10.81 (6.76–17.29)		
Genital tumours				
STERN2002	**IRR** (description of statistical methods unclear)		-	
	High:low[(a)]	2.8 (0.5–15.5)		

(a) *Dose classification as high, medium or low was based on number of exposures and duration of treatment (i.e., a higher cumulative dose was required to classify as high dose at later follow-up times; see full classification table in Appendix Q)*
(b) *The rate after 1985 was an arbitrary time-point chosen to investigate whether the risk changed at longer follow-up points*
(c) *Cohort included those with follow-up interviews after 1992*

Basal cell carcinoma

Five studies[303,307,311,314,316] provided data for the relative risk of BCC at different doses/levels of exposure to PUVA. Similarly to the data for SCC, despite the different methods of analysis used, all of these studies showed a dose-response relationship, with increasing dose/levels of exposure showing incremental rises in the relative risk of skin cancer compared with the reference strata, although the effect size was lower than that for SCC (Table 122).

Based on a method that only counted the first tumour of each type per person, compared with the low dose reference group the observed incidence was 2-times lower[311] or similar[314] in the medium dose group and 2-times higher[311] or 1.7-times higher[314] in the high dose group based on an adjusted standard morbidity ratio, which is linked to the ratio of observed-to-expected incidence.

When comparing multiple dose strata the relative risk or time-to-first tumour (based on a hazard ratio) increased with increasing numbers of exposures, whether using person counts, population rates or total tumour counts. However, this increase was more modest than that seen with SCC.

One study[316] showed that the odds of first cancer at least 10 years after first PUVA exposure increased with increasing cumulative exposure to PUVA during those 10 years.

Table 122: Adjusted relative risk estimates for BCC at different levels of exposure to PUVA

	Multivariate adjusted risk estimate	
Reference	Population rates	Person counts
STERN1984A	-	**Relative SMR (incident tumours after ≥22**

Reference	Multivariate adjusted risk estimate	
		months) Medium:low[(a)] 0.5 (0.2–1.7) High:low[(a)] 2.0 (1.0–4.1) High:medium and low[(a)] 2.2 (1.2–4.4)
STERN1994	-	**RR (relative SMR)** Medium:low[(a)] 0.9 (no CI reported; p>0.1) High:low[(a)] 1.7 (1.1–2.5)
STERN1998A	-	**OR for first cancer after 1985[(b)]** *PUVA exposures* <100 1 100–159 2.0 (1.3–3.1) 160–336 2.1 (1.4–3.1) ≥337 4.7 (3.1-7.3)
NIJSTEN2003A	**IRR (all tumours counted)** *PUVA exposures* < 100 1 100–199 2.35 (1.64–3.38) 200–299 3.76 (2.34–6.06) 300–399 4.63 (2.68–7.98) 400–499 7.62 (4.03–14.43) ≥500 12.69 (6.34–25.40)	**HR (time to first tumour)** *PUVA exposures* <100 1 100–199 1.52 (1.09, 2.12) 200–399 2.26 (1.62, 3.17) ≥400 3.17 (2.13, 4.72)
LIM2005	**IRR** *PUVA exposures* <100 1 100–199 1.80 (1.21–2.70) 200–299 2.00 (1.32–3.03) 300–399 2.81 (1.75–4.51) 400–499 2.93 (1.73–4.98) ≥500 3.65 (2.21–6.03)	-

(a) Dose classification as high, medium or low was based on number of exposures and duration of treatment (i.e., a higher cumulative dose was required to classify as high dose at later follow-up times; see full classification table in Appendix Q).
(b) The rate after 1985 was an arbitrary time-point chosen to investigate whether the risk changed at longer follow-up points

Malignant melanoma

Two studies[315,317] provided data for the relative risk of MM at different levels/durations of exposure to PUVA. Again, an increase in risk was observed with high vs low numbers of PUVA treatments, although this effect was not statistically significant for either all melanoma or invasive melanomas.

However, there was a significant effect of increasing time since first treatment for both all and invasive melanomas (Table 123).

Table 123: Adjusted relative risk estimates for MM (invasive and in situ) at different levels of exposure to PUVA

	Multivariate adjusted risk estimate (incidence rate ratio [IRR]; population rates)	
Reference	**Number of PUVA treatments**	**Years since first treatment (≥15 vs <15)**
STERN1997	**≥250 vs <250** Invasive melanomas: 3.1 (0.9–10.5)	Invasive melanomas: 3.8 (1.1–13.3)

Reference	Multivariate adjusted risk estimate (incidence rate ratio [IRR]; population rates)			
STERN2001	**≥200 vs <200**		All melanomas:	5.9 (2.2–15.9)
	All melanomas:	2.0 (0.9–9.5)	Invasive melanomas:	5.0 (1.6–15.5)
	Invasive melanomas:	1.9 (0.7–4.9)		

A2. PUVA dose (stratified dose subgroups compared with the matched general population)

Seven studies[311-316,318] provided data regarding the relative risk of skin cancer in the PUVA treated cohort at various dose/exposure levels of PUVA compared with the risk in an age-, sex- and geographic location-matched general population. These data were not adjusted for other confounders, including exposure to other psoriasis treatments.

Squamous cell carcinoma

Six studies[311-314,316,318] provided data for the relative risk of SCC at different doses/levels of exposure to PUVA compared with the general population. All of these studies again showed a dose-response relationship, with increasing dose/levels of exposure showing incremental rises in the relative risk of skin cancer compared with the general population; however, in most cases, even the lowest dose group had a significantly increased risk of SCC compared with the general population (Table 124).

The risk of genital tumours was also increased at all PUVA dose levels compared with the general population, with increasing risk at higher dose levels, although the number observed in each subgroup were low, making the precision if the estimate poor[318].

Table 124: Relative risk of SCC in PUVA patients stratified by exposure level compared with the general population

Reference	Standardised morbidity ratio	
	Population rates	**Person counts**
STERN1984A	**All incident tumours after ≥22 months**	**All incident tumours after ≥22 months**
	Low 4.1 (2.3-6.8)	Low 2.2 (0.9-4.3)
	Medium 22.3 (13.5-34.1)	Medium 14.4 (7.6-24.6)
	High[(a)] 56.8 (42.7-74.2)	High[(a)] 31.6 (21.3-45.1)
STERN1988A		**All incident tumours after ≥58 months**
		<160 5.3 (3.6-7.6)
		160-199 25.5 (13.6-43.6)
		200-259 37.5 (23.5-56.7)
		260+ 62.5 (35.0-103.1)
		First tumour after ≥58 months
		<160 4.2 (2.6-6.4)
		160-199 22.2 (10.6-40.9)
		200-259 32.1 (18.7-51.4)
		260+ 50.1 (24.9-89.5)
STERN1994	Low 10.6 (8.5-13.2)	Low 5.0 (3.6-6.9)
	Medium 23.6 (18.0-31.1)	Medium 13.4 (9.3-19.3)
	High[(a)] 83.0 (72.1-95.5)	High[(a)] 32.8 (26.2-41.0)
STERN1998A	<100 5.1 (3.5-7.2)	
	100-159 8.4 (5.6-12.1)	
	160-336 26.5 (22.2-31.4)	

Reference	Standardised morbidity ratio			
	≥337	68.5 (54.9-84.5)		
Genital tumours				
STERN1990			Low	17.5 (0.4-97.7)
			Medium	125.0 (15.1-451.5)
			High	285.7 (104.9-621.9)
STERN2002	**After May 1989**[(b)]		**After May 1989**[(b)]	
	Low	44.4 (5.4-160.5)	Low	44.4 (5.4-160.5)
	Medium	36.1 (0.9-201.1)	Medium	36.1 (0.9-201.1)
	High[(a)]	168.7 (67.8-347-5)	High[(a)]	72.3 (14.9-211.3)
	Total follow-up		**Total follow-up**	
	Low	39.2 (10.7-100.4)	Low	29.4 (6.1-86.0)
	Medium	68.2 (14.1-199.3)	Medium	68.2 (14.1-199.3)
	High[(a)]	283.8 (175.7-433.8)	High[(a)]	148.6 (74.2-266.0)

(a) Dose classification as high, medium or low was based on number of exposures and duration of treatment (i.e., a higher cumulative dose was required to classify as high dose at later follow-up times; see full classification table in AppendixQ)

Basal cell carcinoma

Four studies[311,312,314,316] provided data for the relative risk of BCC at different doses/levels of exposure to PUVA compared with the general population. Again, all of these studies showed a dose-response relationship, with increasing dose/levels of exposure showing incremental rises in the relative risk of skin cancer compared with the general population; however, as with SCC, even the lowest dose group had a significantly increased risk of SCC compared with the general population based on population rates (Table 125).

Table 125: Relative risk of BCC in PUVA patients stratified by exposure level compared with the general population

	Standardised morbidity ratio			
Reference	Population rates		Person counts	
STERN1984A	**All incident tumours after ≥22 months**		**All incident tumours after ≥22 months**	
	Low	1.6 (1.1-2.4)	Low	1.4 (0.9-2.2)
	Medium	1.8 (0.7-3.6)	Medium	0.8 (0.2-2.2)
	High[(a)]	4.5 (2.8-6.9)	High[(a)]	3.2 (1.8-5.3)
STERN1988A			**All incident tumours after ≥58 months**	
			<160	1.6 (1.1-2.2)
			160-199	3.1 (1.3-6.1)
			200-259	5.3 (2.9-9.0)
			260+	7.0 (4.1-11.2)
			First tumour after ≥58 months	
			<160	1.3 (0.8-1.9)
			160-199	3.0 (1.2-6.3)
			200-259	4.8 (3.5-6.5)
			260+	6.9 (3.2-13.1)

Reference	Standardised morbidity ratio			
STERN1994	Low	3.6 (3.0-4.3)	Low	2.1 (1.6-2.7)
	Medium	2.9 (2.0-4.2)	Medium	1.9 (1.2-3.0)
	High[(a)]	6.0 (4.8-7.5)	High[(a)]	3.8 (2.8-5.1)
STERN1998A	<100	1.7 (1.2-2.3)	-	
	100-159	3.9 (3.0-5.0)		
	160-336	4.5 (3.5-5.7)		
	≥337	11.7 (9.3-14.5)		

(a) Dose classification as high, medium or low was based on number of exposures and duration of treatment (i.e., a higher cumulative dose was required to classify as high dose at later follow-up times; see full classification in Appendix Q)

Melanoma

One study[315] provided data for the relative risk of melanoma at different doses/levels of exposure to PUVA compared with the general population. This study only found a significantly higher rate of melanoma in the PUVA cohort compared with the general population among those with the higher level of exposure. Additionally, during the first 15 years of follow-up the risk in the low exposure group was lower than that expected in the general population and was also non-significantly higher than the general population in the high dose group (Table 126).

Table 126: Relative risk of melanoma in PUVA patients stratified by exposure level compared with the general population

	Standardised morbidity ratio	
Reference	Population rates	
STERN1997	**1975-1990[(a)]**	
	<250 treatments	0.7 (0.1-2.5)
	≥250 treatments	3.1 (0.4-11.3)
	1991-1996[(a)]	
	<250 treatments	3.5 (0.7-10.3)
	≥250 treatments	8.9 (2.4-22.8)
	1975-1996	
	<250 treatments	1.3 (0.4-3.1)
	≥250 treatments	5.5 (2.0-12.0)

(a) This stratification by date of follow-up was chosen because an apparent increase in rate of melanoma was noted beginning in 1991 (approximately 15 years after first PUVA treatment).

B. Skin type

Two studies[303,307] provided data regarding the additional skin cancer risk of fair skin (Fitzpatrick phototype I-II) in people with psoriasis who have been treated with PUVA (Table 127).

Both studies demonstrated an increased risk of both SCC and BCC in those with fairer skin. However, the later study[303] showed a less pronounced effect size, which was not statistically significant for BCC. This difference may have been due to the additional covariates adjusted for in this analysis (immunosuppressive therapies, UVB and ciclosporin). Another difference in the analysis was that the lower relative risks were based on population rates and the higher risks were based on total tumour counts. The increased risk was lower for BCC than SCC.

Table 127: Adjusted relative risk estimates for SCC and BCC (invasive) for people with different skin types

Reference	Multivariate adjusted risk estimate (incidence rate ratio [IRR])			
	SCC		BCC	
Total tumour count				
NIJSTEN2003A	Skin type III–VI Skin type I–II	1 2.90 (2.43–3.47)	Skin type III–VI Skin type I–II	1 1.41 (1.15–1.72)
Population rates				
LIM2005	Skin type III–IV Skin type I–II	1 1.76 (1.33–2.31)	Skin type III–IV Skin type I–II	1 1.15 (0.85–1.55)

Skin type classification based on Fitzpatrick system. Type I: always burns, never tans; type II: usually burns, tans with difficulty, type III: sometimes mild burn, gradually tans; type IV: rarely burns, tans with ease; type V: very rarely burns, tans very easily; type VI: never burns, tans very easily.

One study[309] provided data regarding the relative risk of any skin carcinoma in the PUVA treated cohort for different skin types compared with the risk in an age-, sex- and geographic location-matched general population (Table 128). Note that these data were not adjusted for other confounders, including exposure to other psoriasis treatments.

This study showed that there was only a significantly increased risk of skin carcinoma among skin types I-II and not III-IV, although there was still a strong trend towards increased risk in this group.

Table 128: Relative risk of any non-melanoma skin cancer in PUVA patients stratified by skin type compared with the general population

Reference	Standardised morbidity ratio	
	Person counts	
STERN1979	Skin type I-II Skin type III-IV	4.73 (2.12-9.16) 1.89 (1.00-3.67)

C. History of skin cancer

One study provided data regarding the additive risk of prior skin carcinoma at least 3 years before first retinoid use in people with psoriasis who have been treated with both PUVA and retinoids (Table 129).

Table 129: Adjusted relative risk estimates for SCC and BCC determined by prior non-melanoma skin cancer

Reference	Multivariate adjusted risk estimate (incidence rate ratio [IRR]; total tumour counts)			
	SCC		BCC	
NIJSTEN2003	No history of SCC History of SCC	1 4.51 (3.61–5.64)	No history of BCC History of BCC	1 3.44 (2.28–5.21)

One study[309] provided data regarding the relative risk of any skin carcinoma in the PUVA treated cohort for those with and without prior non-melanoma skin cancer compared with the risk in an age-, sex- and geographic location-matched general population (Table 130). Note that these data were not adjusted for other confounders, including exposure to other psoriasis treatments.

This study showed that there was a significantly increased risk of skin carcinoma among both those with and without prior skin carcinoma, but that the risk was much greater for those with a history of skin carcinoma.

Table 130: Relative risk of any non-melanoma skin cancer in PUVA patients with and without prior carcinoma compared with the general population

	Standardised morbidity ratio
Reference	Person counts
STERN1979	Yes: 10.22 (4.78-37.1) No: 1.99 (1.13-3.51)

D. Use of other psoriasis treatments

Seven studies[303,305-307,311,314,316] provided information on the additional risk attributable to other psoriasis treatments among those treated with PUVA. This was presented as the output from a multivariable analysis adjusted for level of exposure to PUVA (and not for PUVA use per se), meaning that the risk estimates do not demonstrate the independent risk of these interventions in isolation from PUVA treatment. The results are summarised in Table 131.

Squamous cell carcinoma

One study[305] showed that using CSA (n=28) in addition to PUVA significantly increased the risk of SCC, but the risk with high level of exposure to CSA was not significantly higher than that for low levels of exposure in another study[303].

High levels of exposure to MTX[303,305,307,314] and UVB[303] also increased the risk of SCC among PUVA-treated individuals; although the odds of first SCC 10 years after first PUVA exposure were non-significantly higher for high vs low MTX exposure[316].

The increased risk with tar and tar plus UVB use was not statistically significant[314,316] and prior exposure to ionising radiation only significantly increased the risk of SCC among those who had low exposure to tar[311].

One study[306] found that oral retinoid use significantly reduced the risk of SCC among PUVA-treated patients when comparing years of use (at least 26 weeks of retinoid treatment) with years of no use (<26 weeks of retinoid treatment) among a subgroup of the PUVA cohort who had been treated with retinoids (n=135). However, when examining the whole cohort, the risk reduction associated with years of high retinoid use was not statistically significant[303].

Basal cell carcinoma

The majority of the evidence suggested that there was no statistically significant increase in risk of BCC among the PUVA cohort linked to high levels of exposure to CSA, MTX, tar alone, tar plus UVB or ionising radiation. However, one study[307] did find a significantly increased risk among those who had high levels of exposure to MTX compared with low exposure; although it should be noted that this study did not adjust for use of CSA. Additionally, the odds for first BCC at least 10 years after first PUVA exposure were significantly higher among those who had high exposure to tar and UVB or to ionising radiation[316].

One study demonstrated a statistically significant increase in risk of BCC among those with high compared with low lifetime exposure to UVB[303].

Table 131: Adjusted relative risk estimates for SCC and BCC based on exposure to systemic agents or tar in addition to PUVA

	Multivariate adjusted risk estimate	
Reference	SCC	BCC
Ciclosporin		
MARCIL2001	**IRR** *(unclear tumour counting)*	-

Reference	Multivariate adjusted risk estimate	
(full cohort)	No CSA use (n=816) 1.0 CSA use (n=28) 3.1 (2.6-3.7)	
MARCIL2001 (nested cohort)	**IRR** *(unclear tumour counting)* 5 years before CSA use (n=28) 1.0 After first CSA use (n=28) 6.9 (4.3-11.0)	-
LIM2005	**IRR** *(population rates)* High (≥3 mo in a given year until 5 y after last use) vs low exposure 1.43 (0.88–2.31)	**IRR** *(population rates)* High (≥3 mo in a given year until 5 y after last use) vs low exposure 1.38 (0.64–2.99)
Methotrexate		
STERN1994	**RR (relative SMR)** *(person counts)* High (>48 mo) vs low 2.1 (1.4-2.8)	**RR (relative SMR)** *(person counts)* High (>48 mo) NS
STERN1998A	**OR for first cancer after 1985**[(a)] *(person counts)* High(>48 mo) vs low 1.3 (0.9-1.9)	**OR for first cancer after 1985**[(a)] *(person counts)* High (>48 mo) vs low 1.1 (0.7-1.5)
MARCIL2001	**IRR** *(unclear tumour counting)* <36 mo 1.0 ≥36 mo 1.7 (1.5-1.9)	-
NIJSTEN2003A	**IRR** *(total tumour count)* ≥36 mo vs low 2.18 (1.79–2.66)	**IRR** *(total tumour count)* ≥36 mo vs low 1.46 (1.17–1.81)
LIM2005	**IRR** *(population rates)* ≥36 mo vs low 1.66 (1.32–2.08)	**IRR** *(population rates)* ≥36 mo vs low 1.24 (0.92–1.67)
UVB (mostly broadband)		
LIM2005	**IRR** *(population rates)* *Cumulative UVB treatments* <300 1 ≥300 1.37 (1.03–1.83)	**IRR** *(population rates)* *Cumulative UVB treatments* <300 1 ≥300 1.45 (1.07–1.96)
Retinoids		
NIJSTEN2003	**IRR** *(total tumour count)* Years of use (≥26 wk) vs years of no use (<26 wk) 0.79 (0.65-0.95)	**IRR** *(total tumour count)* Years of use (≥26 wk) vs years of no use (<26 wk) 0.94 (0.67-1.32)
LIM2005	**IRR** *(population rates)* Year with high exposure (≥26 wk) vs low exposure (<26 wk) 0.88 (0.57–1.35)	**IRR** *(population rates)* Year with high exposure (≥26 wk) vs low exposure (<26 wk) 1.28 (0.80–2.04)
Tar		
STERN1984A	**Relative SMR** *(person counts; incident tumours after ≥22 months)* High:low[(b)] 1.8 (1.0-3.3) *No significant interaction with PUVA: $\chi^2 = 1.7$; p>0.5*	**Relative SMR** *(person counts; incident tumours after ≥22 months)* High:low[(b)] 1.3 (0.6-2.6)
LIM2005	**IRR** *(population rates)* ≥45 mo vs low 1.02 (0.75–1.39)	**IRR** *(population rates)* ≥45 mo vs low 1.28 (0.93–1.76)
Tar/UVB		
STERN1994	**RR (relative SMR)** *(person counts)* High vs low[(c)] NS (no data given)	**RR (relative SMR)** *(person counts)* High vs low[(c)] NS (no data given)

Reference	Multivariate adjusted risk estimate	
STERN1998A	**OR for first cancer after 1985**[(c)] *(person counts)* High vs low[(c)] 1.4 (1.0-2.0)	**OR for first cancer after 1985**[(c)] *(person counts)* High vs low[(c)] 1.5 (1.1-2.0)
Ionising radiation		
STERN1984A	**Relative SMR** *(person counts; incident tumours after ≥22 months)* Some:none (high tar[(b)]) 0.7 (0.3-1.6) Some:none (low tar[(b)]) 2.3 (1.1-4.8) *No significant interaction with PUVA: χ^2 = 2.2; p>0.4*	**Relative SMR** *(person counts; incident tumours after ≥22 months)* Some:none 1.3 (0.7-2.4)
STERN1994	**RR (relative SMR)** *(person counts)* Any vs none NS (no data given)	**RR (relative SMR)** *(person counts)* Any vs none NS (no data given)
STERN1998A	Not reported because not a significant risk factor for SCC in univariate analysis	**OR for first cancer after 1985**[(a)] *(person counts)* Some:none 1.5 (1.1-2.0)

(a) The rate after 1985 was an arbitrary time-point chosen to investigate whether the risk changed at longer follow-up points
(b) Not defined
(c) High tar: topical tar for >45 months; high UVB: >300 treatments

E. Interactions among risk factors among the PUVA treated cohort

Five studies[305,306,309,311,312,318] indicated whether multiple additional risk factors (as well as exposure to PUVA) interacted with each other to further increase risk of SCC or BCC (Table 132). This gives information about whether risk factors modify the effect of other risk factors.

- One study[311] found an interaction between ionising radiation and tar for SCC.
- PUVA dose appeared to increase risk of SCC and BCC to a similar degree regardless of skin type, although skin types I-II are associated with a higher risk than types II-IV compared with the general population[312].
- One study showed that use of CSA was only significantly associated with increased risk of SCC in patients who had high levels of exposure to PUVA[305].
- When analysing only the subset of the PUVA cohort who had also received oral retinoids (n=135), one study found that high tar/UVB exposure, any ionising radiation exposure and high PUVA exposure all significantly increased the risk of both SCC and BCC[306].
- Finally, one study[318] showed that the risk of genital SCCs was increased by exposure to medium- or high-dose PUVA in combination with high dose topical tar/UVB compared with low dose exposure to PUVA and tar/UVB. However, there were very few events in each subgroup, making the precision of these effect estimates very low.

Table 132: Interactions among risk factors for SCC and BCC among the PUVA-treated cohort

	Multivariate adjusted risk estimate	
Reference	**SCC**	**BCC**
Ionising radiation and tar *(person counts)*		
STERN1984A	Yes: χ^2 = 4.72; p<0.05	-
Skin type and PUVA dose *(person counts)*		
STERN1988A	PUVA dose / Skin type: I-II / III-VI <160 1.0 1.0	Nearly identical risk for high vs low dose PUVA in skin type I-II and III-VI groups

Reference	Multivariate adjusted risk estimate			
	160-199	6.1	4.4	Increase in RR vs that expected in general population is ~2.5-fold higher for skin type I-II vs types III and IV with comparable PUVA exposure
	200-259	7.7	4.7	
	260+	11.2	13.2	
CSA exposure and PUVA dose *(unclear tumour counting)*				
MARCIL2001	**≥200 PUVA treatments** (before first CSA or up to 1992 for non-users)			
	Non-user		1.0	
	CSA user		3.5 (2.9-4.2)	
	≤200 PUVA treatments (before first CSA or up to 1992 for non-users)			
	Non-user		1.0	
	CSA user		1.2 (0.7-2.2)	
	No CSA and ≤200 PUVA treatments		1.0	
	CSA and ≥200 PUVA treatments		9.1 (7.4-11.3)	
Tar/UVB exposure and PUVA dose *(population counts)*				
STERN2002	**Genital tumours**			
	Low PUVA[(a)], low tar/UVB[(b)]		1	
	Medium PUVA, high tar/UVB		8.8 (0.9-85.1)	
	High PUVA, high tar/UVB		4.5 (1.3-16.1)	
Retinoid use and tar/UVB exposure *(total counts)*				
NIJSTEN2003	High tar and/or UVB[(b)]		2.42 (2.00-2.93)	High tar and/or UVB[(b)] 3.34 (2.32-4.79)
Retinoid use and ionising radiation exposure *(total counts)*				
NIJSTEN2003	Ionising radiation vs none		3.17 (2.06-4.89)	Ionising radiation vs none 8.42 (4.51-15.73)
Retinoid use and PUVA exposure *(total counts)*				
NIJSTEN2003	< 200		1	< 200 1
	200–499		3.36 (2.34-4.85)	200–499 1.17 (0.78-1.78)
	>499		7.26 (4.91-10.75)	>499 2.65 (1.62-4.36)

(a) Dose classification as high, medium or low was based on number of exposures and duration of treatment (i.e., a higher cumulative dose was required to classify as high dose at later follow-up times; see full classification table in Appendix Q)

(b) High tar: topical tar for >44 months; high UVB: >300 treatments

9.7.552 Evidence statements

A. PUVA dose

In people with psoriasis treated with PUVA:

- Risk of non-melanoma skin cancer increases with PUVA dose/exposure [7 studies[303,305,307,311,314,316,318]; 1380 participants; very low to moderate quality evidence]
- The increase is greater for SCC than BCC, but the difference between high and low dose is significant for both carcinoma types [6 studies[303,305,307,311,314,316]; 1380 participants; low to moderate quality evidence]

- The risk of genital SCC was also greater among those exposed to high vs low levels of PUVA, although this result was non-significant and imprecise owing to the low incidence observed [1 study[318]; 892 participants; very low quality evidence]
- The risk of SCC and BCC was statistically significantly higher than that in the general population even among those in the lowest dose/exposure group, suggesting that any level of exposure to PUVA confers increased risk [6 studies [311-314,316,318]; 1380 participants; very low to low quality evidence]. Note that the estimates for genital SCC were very imprecise and the effect estimate for the low-dose group compared with the general population was non-significant at the earlier follow-up point [2 studies [313,318]; 892 participants; very low to low quality evidence].
- The risk of malignant melanoma shows a non-significant increased incidence at high compared to low numbers of PUVA exposures, but a significant effect of time since first treatment was demonstrated [2 studies[315,317]; 1380 participants; very low quality evidence]
- The risk of malignant melanoma was significantly higher than the general population over the full follow-up period only among those with high exposure to PUVA. Additionally, during the first 15 years of follow-up, the risk in the low exposure group was lower than that expected in the general population and was also non-significantly higher than the general population in the high dose group [1 study[315]; 1380 participants; very low quality evidence].

B. Skin type

In people with psoriasis treated with PUVA:

- Risk of SCC and BCC is higher among those with skin types I-II compared with types III-IV [2 studies[303,307]; 1380 participants; moderate quality evidence]
- The effect size was greater for SCC than BCC [2 studies[303,307]; 1380 participants; moderate quality evidence]
- The risk of any skin carcinoma was only significantly increased compared with a matched general population among skin types I-II and not III-IV, although there was still a strong trend towards increased risk in this group [1 study [309]; 1380 participants; low quality evidence]

C. History of skin cancer

In people with psoriasis treated with PUVA and retinoids:

- Risk of SCC and BCC was statistically significantly higher among those with prior skin carcinoma at least 3 years before first retinoid use [1 study[306]; 1380 participants; low quality evidence]

In people with psoriasis treated with PUVA:

- The risk of skin carcinoma was significantly increased among both those with and without prior skin carcinoma compared with the general population, but the risk was much greater for those with a history of skin carcinoma [1 study [309]; 1380 participants; low quality evidence].

D. Use of other psoriasis treatments

In people with psoriasis treated with PUVA:

- CSA: Risk of SCC was significantly increased with any use of CSA[305], but the risk of SCC or BCC with high level of exposure to CSA was not significantly greater than that for low levels of exposure[303] [2 studies; 1380 participants; low to moderate quality evidence]
- MTX: Risk of SCC was significantly increased with high levels of MTX exposure (>36 or >48 months) compared with low exposure [4 studies[303,305,307,314]; 1380 participants; low to moderate quality evidence]; however, the odds of first SCC at least 10 years after first PUVA use were not significantly greater for high vs low exposure to MTX [1 study[312]; 1380 participants; low quality evidence]

- MTX: Risk of BCC was not significantly increased with high levels of MTX exposure compared with low exposure [3 studies[303,312,314]; 1380 participants; low to moderate quality evidence]; however, one study did find a significant difference [1 study[307]; 1380 participants; moderate quality evidence]
- UVB: Risk of both SCC and BCC was significantly greater among people with high compared with low cumulative exposure to UVB [1 study[303]; 1380 participants; moderate quality evidence]
- Retinoids: Use of oral retinoids significantly reduced the risk of SCC [1 study[306]; 135 participants; low quality evidence]; however, this result was not replicated in a later study using a larger sample from the same cohort[1 study [303]; 1380 participants; moderate quality evidence]. There was no significant effect of oral retinoids on risk of BCC [2 studies[303,306]; 1380 participants; low to moderate quality evidence].
- Tar: Use of high levels of tar did not significantly increase the risk of SCC or BCC compared with low tar exposure [2 studies[303,311]; 1380 participants; moderate quality evidence].
- Tar/UVB: Use of high levels of tar/UVB did not significantly increase the risk of SCC or BCC compared with low tar/UVB exposure [1 study[314]; 1380 participants; moderate quality evidence].
- Tar/UVB: Use of high levels of tar/UVB did not significantly increase the odds of first SCC at least 10 years after first PUVA use compared with low tar/UVB exposure, but the odds of first BCC were significantly increased [1 study[316]; 1380 participants; moderate quality evidence].
- Ionising radiation: Prior exposure to any ionising radiation only significantly increased the risk of SCC among those who had low exposure to tar [2 studies[311]; 1380 participants; moderate quality evidence].
- Ionising radiation: Prior exposure to any ionising radiation did not significantly increase the risk of BCC [2 studies[311]; 1380 participants; moderate quality evidence], although the odds of first BCC at least 10 years after first PUVA were significantly higher among those who had been exposed to any ionising radiation[1 study[311]; 1380 participants; moderate quality evidence].

E. Interactions among risk factors among the PUVA treated cohort

In people with psoriasis treated with PUVA:

- There was a significant interaction between tar and ionising radiation for increasing the risk of SCC [1 study[311]; 1380 participants; moderate quality evidence].
- The effect of PUVA dose on the risk of SCC and BCC was not modified by skin type [1 study [312]; 1380 participants; low quality evidence].
- CSA use only significantly increased the risk of SCC among those exposed to high levels of PUVA [1 study [305]; 844 participants; low quality evidence].
- The risk of genital SCCs was significantly increased by exposure to high-dose PUVA in combination with high dose topical tar/UVB compared with low dose exposure to PUVA and tar/UVB [1 study [318]; 892 participants; very low quality evidence].
- Among the subset of the PUVA cohort who had also received oral retinoids, high tar/UVB exposure, any ionising radiation exposure and high PUVA exposure all significantly increased the risk of both SCC and BCC [1 study[306]; 135 participants; low quality evidence].

9.7.6 Biological drugs, ciclosporin, methotrexate, UVB, tar and retinoids

9.7.6.1 Risk vs. no / low exposure

One study[308], which was primarily designed to assess the risk associated with ciclosporin use, also assessed the independent risk for skin malignancies associated with prior exposure to other psoriasis

treatments compared with those who had no/low exposure to these treatments (Table 133). However, there were too few events to meaningfully analyse SCC and BCC separately and it is noteworthy that less than 50% of the cohort completed the full follow-up period. Also note that the duration of follow-up for exposures other that ciclosporin is unclear, but would have been longer than that for ciclosporin as they were administered prior to trial entry. However, 34% of the cohort received other systemic treatments for psoriasis during the follow-up period and these do not appear to be taken into account in the analysis.

9.7.682 Evidence summary

Table 133: Adjusted relative risk estimates for skin cancer based on exposure to systemic agents

Reference	n (%) of cohort exposed	Multivariate adjusted risk estimate (RR[(a)]; tumour counting unclear)			
		All skin malignancies		All non-melanoma skin malignancies	
Ciclosporin					
PAUL2003	1252 (100%)[(b)] *471 (37.6%) high exposure*[(c)]	High vs low[(c)]	2.7 (1.1–6.4)	High vs low[(c)]	3.3 (1.3-8.4)
Methotrexate					
PAUL2003	351 (28%)	Some vs none	2.1 (0.9–5.3)	Some vs none	2.7 (1.1–7.3)
UVB/UVA					
PAUL2003	238 (19%)	Some vs none	0.7 (0.2–1.8)	Some vs none	0.5 (0.1–1.5)
Tar					
PAUL2003	100 (8%)	Some vs none	2.4 (0.7–6.6)	Some vs none	1.9 (0.4–5.7)
Retinoids[(d)]					
PAUL2003	563 (45%)	Some vs none	4.5 (1.5–19.5)	Some vs none	4.6 (0.9–86.1)

(a) From multivariate analysis using standardised incidence ratio (observed/expected) as outcome variable
(b) Note that 100 (8%) had prior exposure to ciclosporin before recruitment
(c) High defined as >2 years exposure; low as ≤2 years
(d) The authors noted that the contribution of retinoids should be interpreted with caution because of possible confounding: they are often used in combination with PUVA and it may be difficult to separate the individual contribution of retinoids. Additionally, the use of retinoids has been advocated in patients experiencing SCC to prevent recurrence which could create confounding by indication[126].

9.7.673 Evidence statements

In people with psoriasis there was a statistically significantly increased risk of all skin malignancies among those who had been treated with:

- High levels of CSA vs low levels [1 study[308]; 1252 participants – 471 high CSA exposure; very low quality evidence]
- Any retinoids vs none [1 study[308]; 1252 participants – 563 had received retinoids; very low quality evidence]

In people with psoriasis there was a statistically significantly increased risk of SCC and BCC among those who had been treated with:

- High levels of CSA vs low levels [1 study[308]; 1252 participants– 471 high CSA exposure; very low quality evidence]
- Any MTX vs none [1 study[308]; 1252 participants – 351 had received MTX; very low quality evidence]

In people with psoriasis there was no statistically significantly increased risk of all skin malignancies among those who had been treated with:

- Any MTX vs none [1 study[308]; 1252 participants – 351 had received MTX; very low quality evidence]
- Any UVB/UVA (without psoralen) vs none [1 study[308]; 1252 participants – 238 had received UVB/UVA; very low quality evidence]
- Any tar vs none [1 study[308]; 1252 participants – 100 had received tar; very low quality evidence]

In people with psoriasis there was no statistically significantly increased risk of SCC and BCC among those who had been treated with:

- Any UVB/UVA (without psoralen) vs none [1 study[308]; 1252 participants – 238 had received UVB/UVA; very low quality evidence]
- Any tar vs none [1 study[308]; 1252 participants – 100 had received tar; very low quality evidence]
- Any retinoids vs none [1 study[308]; 1252 participants – 563 had received retinoids; very low quality evidence]

9.7.7 Risk vs. general population

Two studies[302,308] provided information on the relative risk of skin cancer among people with psoriasis who have been, or are currently being, treated with CSA or NBUVB compared with an age-, sex- and geographic location-matched general population sample based on incidence data. Two studies[319,320] provided data on the relative risk of skin cancer among people with psoriasis who have been exposed to biologics compared with an age- and sex-matched general population sample based on incidence data. The data were stratified into squamous cell carcinoma, basal cell carcinoma and malignant melanoma.

9.7.7.1 CSA

Evidence summary

One study[308] provided information about the risk of skin cancer among those treated with any level CSA compared with the risk in the general population, including the risk in high and low exposure groups (≤2 years vs >2 years treatment; Table 134). However, the observed numbers of BCC and MM were very low.

Table 134: Relative risk of skin cancer in CSA patients compared with the general population

	Standardised incidence ratio*			
Study	**All skin cancer**	**SCC**	**BCC**	**MM**
PAUL2003	All observed cases: 23 6.1 (3.8–9.1)	All observed cases: 15 24.6 (13.8–40.7)	All observed cases: 5 1.8 (0.6–4.1)	All observed cases: 2 4.7 (0.6–17.0)
	Low 4.8 (2.6–8.1) High[(a)] 10.1 (4.6–19.2)	Low 19.2 (8.8–36.5) High 42.7(15.7–93.2)	Low 0.9 (0.1–3.3) High 4.6 (0.9–13.3)	Low 6.2 (0.8–22.5) High 0.0

**Standardised incidence ratio = numbers observed/numbers expected*
(a) Low dose: ≤2 years treatment; high dose: >2 years treatment

Evidence statements

In people with psoriasis treated with CSA:

- the risk of all skin cancer and the risk of SCC were both statistically significantly higher than that expected in the matched general population [1 study[308]; 1252 participants; very low quality evidence]
- the observed number of BCC and MM cases were low and no statistically significant difference in the risk of these types of skin cancer was found compared with that expected in the matched general population [1 study[308]; 1252 participants; very low quality evidence]
- the increased risk of SCC and all skin cancer was significant for those with both high and low levels of exposure to CSA [1 study[308]; 1252 participants; very low quality evidence]

9.7.7.2 NBUVB

Evidence summary

One retrospective study[302] provided information about the risk of skin cancer among those treated with NBUVB or NBUVB and PUVA compared with the risk in the general population (Table 135).

Table 135: Relative risk of skin cancer in NBUVB patients compared with the general population

Study	Standardised incidence ratio*		
	SCC	BCC	MM
NBUVB only			
HEARNE2008	0 (0-4.65)	1.56 (0.57-3.39)	1.05 (0.03-5.86)
NBUVB + PUVA			
HEARNE2008	1.26 (0.15-4.54)	1.90 (1.06-3.13)	1.57 (0.32-4.60)

**Standardised incidence ratio = numbers observed/numbers expected*

Evidence statements

In people with psoriasis treated with NBUVB only:

- There was no statistically significant difference in the risk of SCC, BCC or MM from that expected in the matched general population [1 study[302]; 2130 participants; very low quality evidence]

In people with psoriasis treated with NBUVB and PUVA:

- The risk of BCC was statistically significantly higher than that expected in the matched general population [1 study[302]; 2130 participants; very low quality evidence]
- There was no statistically significant difference in the risk of SCC or MM from that expected in the matched general population [1 study[302]; 2130 participants; very low quality evidence]

9.7.7.3 Biological therapy

Evidence summary

One retrospective study of prospectively gathered data[319] provided information about the risk of skin cancer among those treated with etanercept for up to 48 months compared with the risk in the general population (Table 136). However, general population reference data were only available from USA registries while the exposed group were from Canadian cohorts, so the exposed and unexposed cohorts were not match on geographic location, which will effect sun exposure and skin cancer rates. This confounding variable was not accounted for in the analysis. One prospective study[320] provided information about the risk of skin cancer among those treated with any biological therapy for psoriasis and followed-up for 5 years compared with the risk in the general population

(Table 136). However, prior treatments were not controlled for and all of those who had an event had also been exposed to PUVA and most to ciclosporin. Additionally, the time to first tumour was shorter than a year in the majority of cases, indicating that the biological agent was not causative to the pathology.

Table 136: Relative risk of skin cancer in people treated with etanercept compared with the general population

Study	Standardised incidence ratio*	
	SCC	BCC
Reference group: South-eastern Arizona Skin Cancer Registry		
PAPP2012A	1.08 (0.29-2.76)	0.52 (0.23-1.03)
Reference group: Rochester Epidemiology Project; Minnesota		
PAPP2012A	2.68 (0.72-6.87)	-
Reference group: Dutch General Practice Registry		
VANLUMIG2012	81.4 (39.0-149.8)	12.2 (5.9-22.5)

**Standardised incidence ratio = numbers observed/numbers expected*

Evidence statements

In people with psoriasis treated with etanercept:

- There was no statistically significant difference in the risk of SCC or BCC from that expected in the general population matched for age and sex, but not geographic location [1 study[319]; 506 participants; very low quality evidence]
  - The effect estimate suggested an increase in risk for SCC compared with the rates in Minnesota, which may be a better match in terms of ambient UV exposure to the Canadian cohort than the Arizonan rates [1 study; 506 participants; very low quality evidence][319]
- However, there was a statistically significantly higher risk for people with psoriasis exposed to biological therapies compared with the general population in another study [1 study; 173 participants; very low quality evidence][320]

9.7.8 Economic evidence

No relevant economic evidence was identified.

9.8 Recommendations and link to evidence

Recommendations on risk of skin cancer	**66. Do not use PUVA in people with psoriasis and a genetic predisposition to skin cancer for example, xeroderma pigmentosum or familial melanoma.** **67. Do not use PUVA when other appropriate treatments are available in:** • **people with a personal history of skin cancer or** • **people who have already received 150 PUVA treatments or** • **children.** **68. Use PUVA with caution and consider other treatment options in:** • **people at risk of skin cancer (melanoma and non-melanoma**

	type) (see 'Improving outcomes for people with skin tumours including melanoma' [NICE cancer service guidance]) • **people with lighter skin types, such as skin types I or II on the Fitzpatrick scale** • **people who are likely to require ciclosporin or long-term methotrexate** • **young people.** **69. When considering PUVA for psoriasis (plaque or localised palmoplantar pustulosis) discuss with the person:** • **other treatment options** • **that any exposure is associated with an increased risk of skin cancer (squamous cell carcinoma)** • **that subsequent use of ciclosporin may increase the risk of skin cancer, particularly if they have already received more than 150 PUVA treatments** • **that risk of skin cancer is related to the number of UV exposures.** **70. Offer lifetime skin cancer surveillance to people treated with PUVA who have:** • **had more than 150 PUVA treatments or** • **developed skin cancer.** **71. Document (for example, in a national record) the cumulative number of UV exposures.**
Future research recommendations	**17. What is the risk of skin cancer in people with psoriasis exposed to phototherapy, systemic (including biological) therapies and are there any strategies that can modify or avoid this risk?**
Relative values of different outcomes	Incidence rates for malignancy • Melanoma • Non melanoma – squamous cell carcinoma (SCC)and basal cell carcinoma (BCC) Melanoma is the major cause of death due to skin cancer as a whole so any increase in risk of melanoma is considered of greater significance when compared to risk of SCC or BCC. Non-melanoma skin cancer (SCC and BCC) whilst undesirable, are generally curable; SCC has greater implications than BCC in terms of impact on health as it can be aggressive and metastasise, especially at genital and lip sites, whereas this is rare with BCC. Skin cancers as a whole are common in the UK and therefore any increase in skin cancer incidence is potentially significant.
Trade off between clinical benefits and harms	PUVA is associated with an increased risk of skin cancer, both non-melanoma and melanoma. The risk is most marked for squamous cell carcinoma, is consistent across different studies and populations, is dose-related, does not reduce on stopping PUVA, and persists for a

lifetime. There is no absolute safe dose. The current belied that fewer than 200 treatments is safe practice is not supported by the data. This led the GDG to recommend that cumulative dose of PUVA should be documented.

There is a particular risk of genital SCC, which has been addressed by a change in clinical practice with the introduction of genital shielding in the 1990s.

People with skin types 1 and 2 are at a greater risk of squamous cell carcinoma than people with skin types 3 and 4, but there is a risk for all skin types. Subsequent treatment with ciclosporin further increases the risk and long-term treatment with methotrexate also increases the risk, although it was unclear whether the risk was associated with methotrexate exposure before or after PUVA. However, it is likely that methotrexate use after PUVA, as with ciclosporin, is also a greater risk than before PUVA because the mechanism is widely though to involve immunosuppressive treatments after PUVA inducing the emergence of skin cancer.

Regarding the exposure to both PUVA and UVB there was limited data and mainly for broadband UVB, so the GDG agreed not to include UVB as a known additional risk factor for skin cancer in people receiving PUVA.

The GDG noted that the relative and absolute risk of SCC compared with the general population increased markedly once more than 160 PUVA exposures had been received, so it was agreed that it is unreasonable to expose people to greater than 160 treatments.

When considering the place of PUVA for the treatment of psoriasis, the GDG considered the efficacy and adverse effects of UVB as those patients who are suitable for PUVA are also likely to be suitable for UVB. In relation to efficacy, clearance rates are probably equivalent; the 2-3 week improved time to clearance, and 1.55 relative risk of relapse with oral PUVA were not felt to offset the increased inconvenience, risks (both short-term in relation to taking an oral psoralen and long-term risk in relation to skin cancer) and cost when compared to NBUVB. Bath PUVA was less effective that NBUVB in terms of time to clearance and relapse rates. The GDG concluded that it would be difficult to justify use of PUVA in patients who had not already failed UVB.

There were no studies investigating the efficacy of PUVA in people who had failed UVB to be confident that PUVA would be effective in these individuals. The GDG noted that the efficacy rates of oral PUVA were high in terms of clearance (and may be better than methotrexate or ciclosporin or some of the biological drugs). However, PUVA is not an intervention that can be used to maintain remission (relapse rate 45% by 6-12 months) and the risks of skin cancer are clinically relevant, life long and compounded by future use of other treatments that are used to treat psoriasis, even accepting that the morbidity and mortality rates from skin cancer are low, that some of the data relates to very high doses of PUVA over prolonged periods of time and that the risks in relation to skin cancer or other risks of alternative treatment options

such as methotrexate or biological therapy are poorly documented. The GDG concluded that for most people who had failed or relapsed rapidly with NBUVB, use of PUVA may not be justified if other treatments could be used.

The GDG did not wish to limit treatment options by making a recommendation not to use PUVA at all, but felt it important to highlight the risks of PUVA and groups at particular risk and offer PUVA only when other options had been actively considered and rejected.

Healthcare professionals should fully explain the risks of PUVA treatment including the absolute risk, and the potential implications of PUVA in relation to future treatment options. Fully informed written consent should be obtained.

The GDG wished to ensure that the risk of significant PUVA-related harm was minimised by recommending those already in high risk groups are offered annual surveillance for skin cancer.

When considering the role of local PUVA for palmoplantar pustulosis, there are very few effective interventions for this condition and the area of skin exposed to UVA is very limited, hence the clinical benefit of local PUVA, if the impact of palmoplantar pustulosis is high, may be justified.

The GDG noted that the long term risks of PUVA were relatively well documented compared to those associated with the alternative options including systemic biological and non-biological therapies; the GDG were aware of long term registries comparing the risks of these different interventions and agreed that participation should be encouraged.

Only limited data were available for UVB. It was noted that data up to 5 years is now available for NBUVB and no significant increase in skin cancer risk is reported, whereas risks associated with PUVA were evident by this time point. The GDG discussed the evidence that after NBUVB the risk of BCC was more increased than SCC, in contrast to PUVA. The GDG considered that in light of experience with PUVA where there may be a prolonged lag period between use of PUVA and development of skin cancer, and that the risk is dose-related, it is important that all patients receiving phototherapy of any kind should have the cumulative amounts of phototherapy recorded carefully.

From GDG knowledge, people with a personal history of skin cancer or predisposition to skin cancer (for example, xeroderma pigmentosum) should not be offered PUVA. It was also noted that risk rates reported in more recent studies are likely to exclude groups of people already at risk of skin cancer (both non-melanoma and melanoma). The GDG agreed that alternative treatment strategies to PUVA should be sought in younger people due to the lifetime risk of skin cancer and impact on potential future treatment options. Whilst the GDG did not review data pertaining to genetic predisposition as it was outside of the remit of the scope, the GDG agreed an important consensus safety recommendation. People with a personal history of skin cancer or

	predisposition to skin cancer (for example, xeroderma pigmentosum) should not be offered PUVA.
Economic considerations	No economic evidence was available to inform the GDG on how the risk of skin cancer may impact the relative cost-effectiveness of different interventions including systemic and photo therapies used in the treatment of psoriasis. In the absence of such information, the GDG considered the balance between short term gains in the form of disease improvement and increased long term risks of different skin cancers. For most patients, the GDG did not consider the increased long term risks of psoriasis treatments (in terms of associated morbidity, mortality or costs) to outweigh the benefits in the short term, but did highlight the importance of carefully communicating a treatment's potential benefits and harms to patients. However, the evidence showed that some patients may be at even higher risk given a personal history of skin cancer, skin type, previous and future treatments. In particular they also discussed the synergistic effect certain treatments have when combined or used in immediate succession (e.g. PUVA immediately preceded or followed closely by ciclosporin) and felt that this should be avoided because the risks far outweighed the potentially benefits. The GDG considered that different skin cancers have different prognoses and treatment costs. Basal cell carcinoma and squamous cell carcinoma rarely metastasise or lead to death, but they can cause considerable morbidity. The estimated cost of removing BCC and SCC vary depending on the setting of treatment, from £85 in primary care[321] to £132 in secondary care as an outpatient procedure (HRG JC07Z)[277]. In order to ensure patients are not exceeding reasonably safe doses of phototherapy, the GDG considered it important to document cumulative doses. They believed that benefit of documentation, arising from cancers and associated morbidity and mortality avoided, was likely to represent good value for NHS resources.
Quality of evidence	There was a lack of data for a number of interventions and subgroups: • No subgroup data for disease severity, age at first exposure, smoking and alcohol. Nor were there data on oral versus bath PUVA. • No studies designed specifically to investigate the risk associated with methotrexate, UVB or tar • There was insufficient data to assess the risk of skin cancer associated with exposure to NBUVB or biologics as the available studies had a relatively short follow-up time and were not controlled for confounding factors such as prior treatments and in one[319] the reference cohort was not from the same geographic location so different natural UV exposure could confound the findings. • Future reports on the NBUVB cohort are awaited. The GDG noted that there is a suggestion mainly from animal studies that biologics may have a carcinogenic effect. The ideal study design to address this question would have been a cohort study designed specifically to compare people with psoriasis not treated with an intervention with people with psoriasis treated with an intervention. This would help to determine the specific risk associated

with the intervention independent of any risk associated with psoriasis per se. However, this is not a feasible design. Therefore, for all studies the unexposed cohort was a general population sample and so would have included a proportion with psoriasis and potentially with exposure to the interventions beings assessed as risk factors (e.g., PUVA or ciclosporin).

All of the studies also had a high level of outcome surveillance bias as there is likely to be more complete ascertainment of skin cancer cases among the exposed cohort who were actively followed-up and examined compared with the general population where diagnoses may be missed.

In addition, the majority of the data was derived from the Stern cohort from 16 centres in the USA, collected since the 1970s and followed-up for many years. The GDG discussed that the standard PUVA regimen in the USA differs from the UK and that the baseline SCC incidence is higher in the USA. There is a higher proportion of people with skin type 3 and above in this cohort. Whilst the GDG agreed that data from a UK cohort would be more relevant they agreed that the Stern et al data set was a very large study with a long follow up period. The GDG were aware of data from a retrospective European PUVA study (Lindelof 1991) with approximately 7 year follow-up that did not meet the inclusion criteria (because the population was only 50% psoriasis and it was a retrospective cohort). It was noted that the Lindelhof et al study also demonstrated a dose-dependent increase in the risk of squamous cell skin cancer although a dose-dependent increase in the risk of squamous cell cancer and a greater risk in those with fairer skin but the magnitude of the risk was lower than that in the Stern cohort.

It was noted that the stratification of PUVA dose varied between the studies in the Stern cohort and it was unclear whether the thresholds for stratification were pre-specified or had been chosen based on the data, which could lead to bias.

The GDG also noted that the results from the Stern cohort may be biased by the fact that 39 patients out of the 1380 had a history of skin cancer before PUVA (so the reported rates may not related to true incidence) and this was not controlled for in all analyses. According to current practice these individuals would not have been offered PUVA.

Due to the long-term nature of this study, less than 80% of the original cohort remained after 1984. The authors report that most of the loss was due to death and consistent with the expected rate. Withdrawal and loss to follow up were acceptable, but reasons for loss were unclear. Therefore we do not know if the characteristics of those lost are the same as those who remained in the study and whether this could have biased the results.

Studies differed in their method of recording tumour incidence. Some used a total count where each tumour is counted; others used person counts, whereby the first tumour of a specific type is counted. The latter tends to be a conservative estimate of risk. Other studies report

	population counts, including reporting only the first tumour in a year in an individual. This approach may limit the influence of cohort members who may be outliers (i.e. those rare individuals who develop a large number of tumours per year) by restricting to annual incidence. This last method was also in accordance with the method of recording in the national registries that were used to estimate the expected incidences in the unexposed cohort in the Stern studies. Some studies included pre-malignant skin cancers, and so the risk of skin cancer would potentially have been over-estimated in these studies compared with studies that did not include pre-malignant skin cancers. Additionally it was apparent that genital sites are especially vulnerable and current practice is to shield the genital area during exposure to PUVA. The early use of PUVA in the Stern cohort will have been prior to practice change to use genital shielding, and therefore an overestimate of the current risk associated with PUVA. There are no data on the risk when genital tumours are excluded, although the studies looking at genital tumours specifically did adjust for variation in genital shielding between enrolled centres. The studies also varied in the statistical analysis, with many of the earlier studies not performing a regression analysis to control for confounders, instead matching the exposed and unexposed cohorts for age, sex and geographic location. Only one study used Cox proportional hazards to take account of time in the analysis, although other studies did control for time in the analysis by different methods. Even when regression analysis was performed the number of confounders that were adjusted for varied between the studies and was not complete in any: use of UVB and history of skin malignancy were rarely controlled, although age and geographic residence were used as surrogate markers of cumulative sun exposure The GDG noted specific biases in the following studies: • Stern 1997 study on melanoma: the threshold for the different time periods appeared to have been selected based on the data and the observed increase in incidence, which introduces bias • Marcil: there were very few people receiving ciclosporin • Paul 2003: this study was primarily designed to assess the risk of ciclosporin and had a high attrition rate. The duration of follow up for PUVA is unclear. 34% of the cohort received their systemic treatment during the follow up period, and this did not seem to be taken into account in the analysis. Due to these major limitations the GDG gave little weight to this study, apart from the ciclosporin findings.
Other considerations	One of the later follow-up studies in the Stern PUVA cohort demonstrated no independent carcinogenic effect of UVB, topical tar or ionising radiation, which conflicted with earlier findings. This may be because PUVA is the main carcinogen and is as more is received it outweighs the impact of other factors.

1

10 Systemic therapy

Systemic non-biological therapy[322] is invariably indicated in patients with life-threatening forms of unstable psoriasis such as generalised pustular psoriasis and erythroderma; these are rare. Systemic non-biological therapy is more commonly used in people with extensive stable plaque psoriasis where topical therapy would be impractical and potentially unsafe and where phototherapy is not appropriate or has failed (see chapter 6). People with localised plaque psoriasis associated with significant functional impairment and/or psychological distress (for example severe nail disease, hand and foot involvement), palmo-plantar pustulosis and extensive 'guttate type' psoriasis may also benefit from systemic non-biological therapy. The presence of psoriatic arthritis can have a major influence on when systemic non-biological therapy is considered in the treatment pathway for skin psoriasis and the choice of agent is also critical since acitretin and fumaric acid esters have no benefit in psoriatic arthritis, whereas methotrexate and ciclosporin do. Accurate UK data on the proportion of people with psoriasis who are treated with systemic non-biological therapy is not available. In one US based study, the proportion of people with BSA >10% was 5.25% of all people with [11] and could be used as a crude surrogate indicator of those potentially eligible for systemic non-biological therapy but is likely to be inaccurate.

Ciclosporin (CSA), methotrexate (MTX), acitretin and fumaric acid esters are the most commonly used systemic therapies to treat psoriasis. In other inflammatory diseases, induction of remission and maintenance therapy are often considered separately. Recent European guidelines for the treatment of psoriasis have adopted this approach in considering achievement of PASI 75 over 12-16 weeks[322]. In practice, once satisfactory control is achieved, the same treatment is continued at the minimal effective dose in order to maintain disease control and quality of life. Ciclosporin is the exception to this given the predictable nephrotoxic effects of the drug with continuous use, and is not generally considered suitable for long-term disease management. All the interventions can be complicated by poor tolerability, short and long-term toxicity and poor or inadequate efficacy. Supplementary treatment with topicals is commonly required.

Which agent to choose is influenced by multiple factors and must be tailored to the needs of the individual. The type and pattern of psoriasis, extent of involvement and whether or not rapid control is necessary are important. For example, stable chronic plaque psoriasis requires a very different treatment strategy to generalised pustular psoriasis. The presence of psoriatic arthritis, co-morbidities, age, conception plans, preferences of patient and clinician, logistical issues around safe drug administration and monitoring as well as many other factors also need to be taken into account. Nevertheless, it is useful to review the evidence on the relative efficacy and safety of the available agents to inform the decision-making process.

The evidence review excluded data on fumaric acid esters as this is not licensed for any indication in the UK and therefore falls outside the agreed standard operating procedures for NICE guidelines.

The GDG agreed to ask the following question: in people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of systemic methotrexate, ciclosporin and acitretin?

10.1 Methodological introduction

A literature search was conducted for randomised controlled trials or systematic reviews that compared the efficacy and safety of methotrexate, ciclosporin and acitretin with each other or with placebo/no treatment for the induction or maintenance of remission in people with psoriasis. Comparisons of different doses of a particular treatment and of different maintenance schedules were also sought. Additionally, long-term safety data was sought from cohort or case control studies.

No time limit was placed on the literature search and there were no limitations on duration of follow-up. Indirect populations were excluded as were studies with a sample size of less than 10.

The outcomes considered were:

- PASI75
- PASI50
- Change in PASI (mean improvement) or final PASI as a surrogate outcome
- Clear or nearly clear (minimal residual activity[MRA]/PASI>90/0 or 1 on PGA)
- Improved (for PPP population only)
- Time-to-relapse (loss of PASI50)
- Time-to-remission/max response
- Change in DLQI
- Severe adverse events
  - Specific adverse events were assessed for each intervention (methotrexate: hepatotoxicity, marrow suppression and pneumonitis; acitretin: hyperlipidaemia, hepatotoxicity, skeletal AEs and cheilitis; ciclosporin: renal impairment, hypertension, gout and hyperuricaemia)
- Withdrawal due to toxicity

Twenty eight RCTs were found that addressed the question and were included in the review. There was no suitable long-term observational data and no studies were available that assessed systemic non-biological therapy in an exclusively paediatric population. The studies differed in terms of the disease severity stated as an inclusion criterion (Table 137):

Table 137: Disease severity inclusion and dosing schedules of included studies

Reference ID	Disease severity	Comparison	Dose and schedule
Induction of remission			
BERBIS 1989	Severe psoriasis (66.7% plaque, 9.1% guttate, 13.6% pustular, 3.0% erythrodermic, 4.5% palmoplantar pustulosis, 3.0% acrodermatitis continua)	Acitretin dosing	Acitretin: increasing (10 up to 50 mg/day) vs decreasing (50 down to 10 mg/day) or constant (30 mg/day) dose schedule *Note: for this study the increasing dose arm was used as the control arm as this reflects current clinical practice in the UK*
CHRISTOPHERS 1992	Severe generalised chronic plaque psoriasis PASI≥15	CSA dosing (induction)	CSA: 1.25 vs 2.5 mg/kg/day (initial doses but could be doubled if ineffective)
ELLIS 1986	Severe chronic large plaque-type psoriasis vulgaris >20% BSA involvement	CSA vs placebo (induction)	CSA: 14 mg/kg/day (plus open phase)
ELLIS 1991	Chronic plaque psoriasis affecting >25% BSA, or disabling psoriasis	CSA vs placebo (induction)	CSA: 3, 5 or 7.5 mg/kg (plus open dose adjustment phase)
ERKKO 1998	Clinically defined palmoplantar pustulosis of the palms and/or soles with at least 20 whitish-yellow pustules of diameter at least 1mm	CSA vs placebo for PPP	CSA: 1 mg/kg/day (1 month double blind); plus 11 month open phase (dose increased by 1 mg/kg/day if no response up to a maximum of 4 mg/kg/day)
FLYTSTROM	Moderate-to-severe	MTX vs CSA	MTX: 7.5 mg/wk (3-divided dose) up to 15

Reference ID	Disease severity	Comparison	Dose and schedule
2008	chronic plaque psoriasis: classified by physician and patient		mg/wk (plus folic acid) CSA: 3 mg/kg/d (divided into 2 doses) up to 5 mg/kg/d
GOLDFARB 1988	BSA>10% or disabling disease	Acitretin vs placebo	10, 25, 50 or 75 mg/day acitretin (plus open phase)
GUENTHER 1991	Large plaque psoriasis BSA ≥25% and PASI ≥12	CSA vs placebo (induction)	CSA: 2.5-5 mg/kg/day
GUMUSEL 2011	Moderate-to-severe psoriasis BSA >10% and PASI ≥10 and NAPSI >10	MTX vs CSA	MTX: 15 mg/wk (initial dose) reduced to 10 mg/wk after 3 months (plus folic acid) CSA: 5 mg/kg/d reduced to 2.5-3.5 mg/kg/d
HEULE 1988/ VANJOOST 1988A	Chronic plaque psoriasis PASI≥20	CSA vs placebo (induction)	CSA: ~5-7 mg/kg/day (plus open phase)
HEYDENDAEL 2003	Moderate-to-severe chronic plaque psoriasis: PASI ≥8	MTX vs CSA	MTX: 15 mg/wk (3-divided dose) up to 22.5 mg/wk (folic acid use not specified) CSA: 3 mg/kg/d (divided into 2 doses) up to 5 mg/kg/d
HO 2010	BSA ≥20% Plaque psoriasis	MTX vs placebo	MTX: 2.5-5.0 mg/wk to assess safety then 10 mg/wk up to 30 mg/wk Folic acid supplement (MTX arm only)
KINGSTON 1987	BSA>20%	Acitretin vs placebo	10, 50 or 75 mg/day acitretin (plus open phase)
LASSUS 1987	Severe psoriasis (87.5% plaque, 5% pustular and 7.5% erythrodermic)	Acitretin vs placebo	10, 25 or 50 mg/day acitretin (plus open phase)
MEFFERT 1997	Psoriasis vulgaris PASI ≥8	CSA vs placebo (induction)	CSA: 1.25 or 2.5 mg/kg/day (plus open phase)
REITAMO 1993	Clinically defined palmoplantar pustulosis of the palms and/or soles with at least 20 whitish-yellow pustules of diameter at least 2mm	CSA vs placebo for PPP	CSA: 2.5 mg/kg/day (1 month double blind); plus 2 month open phase (dose increased by 1.25 mg/kg/day if no response)
SANDHU 2003	Severe psoriasis (73.3% plaque and 26.6% erythrodermic) BSA >40%	MTX vs CSA	MTX: 0.5 mg/kg/wk (folic acid use not specified) CSA: 3 mg/kg/d (divided into 2 doses) up to 4 mg/kg/d Doses tapered once PASI75 reached (maintenance)
SAURAT 2008	Moderate-to-severe plaque psoriasis: BSA ≥10% and PASI ≥10	MTX vs placebo	MTX: 7.5 mg increased to 25 mg/wk as needed and tolerated Folic acid supplement (both arms)
Maintenance of remission			
CHAIDEMENOS 2007	Moderate-to-severe chronic plaque psoriasis PASI≥8	CSA regimens for maintenance	Intermittent CSA: abruptly stopped ciclosporin after induction, then received additional 12-week course on relapse Continuous CSA: tapered by 0.5mg/kg/day bi-monthly down to maintenance level

Reference ID	Disease severity	Comparison	Dose and schedule
			(lowest marginally effective dose)
COLOMBO 2010	Chronic plaque psoriasis treated with continuous ciclosporin (severity not stated) Achieved remission (PASI75) during induction therapy	CSA vs placebo (maintenance)	CSA: 5 mg/kg/day at weekends only
ELLIS 1995	Chronic plaque psoriasis affecting >25% BSA, or disabling psoriasis	CSA vs placebo (maintenance)	CSA: 1.5 or 3 mg/kg/day (no dose adjustment)
HO 1999	Plaque psoriasis unresponsive to topical therapies (mean baseline PASI 24.5)	CSA regimens for maintenance	Intermittent CSA: abruptly stopped ciclosporin after induction, then received additional course on relapse Continuous CSA: tapered by 1 mg/kg daily each week until stopping within 4 weeks, then received additional course on relapse
HO 2001	Plaque psoriasis Requiring systemic therapy (mean BSA at baseline approximately 17%)	CSA regimens for maintenance	Intermittent CSA: abruptly stopped ciclosporin after induction, then received additional course on relapse Continuous CSA: tapered by 1 mg/kg daily each week until stopping within 4 weeks, then received additional course on relapse
LABURTE 1994	Severe chronic plaque psoriasis PASI ≥18	CSA dosing (induction and maintenance)	CSA: 2.5 vs 5.0 mg/kg/day (initial doses during phase 1); patients achieving remission entered a maintenance phase (2.5 vs 5.0 mg/kg/day: 5 mg tapered to 2.5 over 3 months and dose tapered in all from month 9-12)
OHTSUKI 2003	Severe psoriasis PASI>20	CSA regimens for maintenance	**'Continuous' CSA:** Following induction of remission with 3-5 mg/kg/day ciclosporin the dose was reduced by 0.5-1.0 mg/kg/day every week and maintained as the lowest effective dose (in the range 0.5-3 mg/kg/day) If relapse occurred, the dose was increased to 3-5 mg/kg/day until remission was achieved, and the same procedure was repeated. **'Intermittent' CSA:** Following induction of remission with 3-5 mg/kg/day ciclosporin the dose was reduced by 0.5-1.0 mg/kg/day every other week followed by withdrawal. During withdrawal, topical steroids (10 g/day or less) of strong or medium potency were applied If relapse occurred, the dose was increased to 3-5 mg/kg/day until remission was achieved. Treatment was withdrawn on remission and topical steroids were again applied.
OZAWA 1999	Psoriasis vulgaris with PASI	CSA regimens	**'Continuous' CSA:** Following induction of

Reference ID	Disease severity	Comparison	Dose and schedule
	>20; psoriatic arthritis; generalised pustular psoriasis; erythrodermic psoriasis	for maintenance	remission with 3-5 mg/kg/day ciclosporin the dose was reduced by 0.5-1.0 mg/kg/day every week and maintained as the lowest effective dose (in the range 0.5-3 mg/kg/day) If relapse occurred, the dose was increased to 3-5 mg/kg/day until remission was achieved, and the same procedure was repeated. **'Intermittent' CSA:** Following induction of remission with 3-5 mg/kg/day ciclosporin the dose was reduced by 0.5-1.0 mg/kg/day every other week followed by withdrawal. During withdrawal, topical steroids (10 g/day or less) of strong or medium potency were applied If relapse occurred, the dose was increased to 3-5 mg/kg/day until remission was achieved. Treatment was withdrawn on remission and topical steroids were again applied.
SHUPACK 1997	BSA>12% or disabling psoriasis that impairs daily activities	CSA vs placebo (maintenance)	CSA: 3 mg/kg/day (with dose adjustment) *Note: initial randomisation to 1.5 mg/kg arm stopped after 7 people were recruited owing to evidence suggesting lack of efficacy (so results reported for 3 mg/kg/day vs placebo only)*
THACI 2002	Chronic plaque type psoriasis PASI ≥12.	CSA vs placebo (maintenance)	CSA: lowest effective dose

The systematic review protocol specified clear or nearly clear disease as an outcome and this was defined as either: i) minimal residual activity; ii) PASI90; or III) 0 or 1 on PGA. The data from the studies identified for this section showed that PASI90 and 0 or 1 on PGA were not equivalent outcomes. PASI90 was found to be a more stringent criterion of response. For this reason both outcomes are reported separately.

10.1.11 Methotrexate vs placebo for induction of remission

10.1.12 Evidence profile

Table 138: Evidence profile comparing methotrexate vs placebo for induction of remission

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Placebo	Relative (95% CI)	Absolute	
PASI90 – Incremental MTX dosing (7.5 up to 25 mg/wk) (follow-up 16 weeks)											
1 Saurat 2008	randomised trials	no serious limitations	no serious inconsistency	serious[a]	very serious[b]	Folic acid also given	15/104 (14.4%)	6/52 (11.5%)	RR 1.25 (0.52 to 3.03)	29 more per 1000 (from 55 fewer to 234 more)	⊕OOO VERY LOW
Clear/nearly clear on PGA – Incremental MTX dosing (7.5 up to 25 mg/wk) (follow-up 16 weeks)											
1 Saurat 2008	randomised trials	no serious limitations	no serious inconsistency	serious[a]	no serious imprecision	Folic acid also given	33/104 (31.7%)	6/52 (11.5%)	RR 2.75 (1.23 to 6.14)	202 more per 1000 (from 27 more to 593 more)	⊕⊕⊕O MODERATE
PASI75 – Incremental MTX dosing (7.5 up to 25 mg/wk or 10 up to 30 mg/wk) (follow-up 4-6 months)											
2 Ho 2010 Saurat 2008	randomised trials	no serious limitations[c]	no serious inconsistency	serious[d]	no serious imprecision	Folic acid also given	51/123 (41.5%)	13/69 (18.8%)	RR 2.26 (1.34 to 3.83)	237 more per 1000 (from 64 more to 533 more)	⊕⊕⊕O MODERATE
PASI50 – Incremental MTX dosing (7.5 up to 25 mg/wk or 10 up to 30 mg/wk) (follow-up 4-6 months)											
2 Ho 2010 Saurat 2008	randomised trials	no serious limitations[c]	no serious inconsistency	serious[d]	no serious imprecision	Folic acid also given	83/123 (67.5%)	20/69 (29%)	RR 2.33 (1.58 to 3.43)	386 more per 1000 (from 168 more to 704 more)	⊕⊕⊕O MODERATE
PASI change/final score – Incremental MTX dosing (7.5 up to 25 mg/wk or 10 up to 30 mg/wk) (follow-up 4-6 months; better indicated by lower values)											

Quality assessment							Summary of findings				
2 Ho, 2010 Saurat, 2008	randomised trials	no serious limitations [e]	no serious inconsistency	serious[d]	no serious imprecision	Folic acid also given	123	69	-	MD 6.69 lower (9.48 to 3.90 lower)	⊕⊕⊕O MODERATE
Severe adverse events – Incremental MTX dosing (7.5 up to 25 mg/wk) (follow-up 26 weeks)											
1 Saurat, 2008	randomised trials	no serious limitations	no serious inconsistency	serious[a]	very serious[b]	Folic acid also given	1/110 (0.9%)	1/53 (1.9%)	RR 0.48 (0.03 to 7.55)	10 fewer per 1000 (from 18 fewer to 124 more)	⊕OOO VERY LOW
Withdrawal due to toxicity – Incremental MTX dosing (7.5 up to 25 mg/wk) (follow-up 26 weeks)											
1 Saurat, 2008	randomised trials	no serious limitations	no serious inconsistency	serious[a]	very serious[b]	Folic acid also given	6/110 (5.5%)	1/49 (2%)	RR 2.67 (0.33 to 21.61)	34 more per 1000 (from 14 fewer to 421 more)	⊕OOO VERY LOW
Raised liver enzymes – Incremental MTX dosing (7.5 up to 25 mg/wk) (follow-up 26 weeks)											
1 Saurat, 2008	randomised trials	no serious limitations	no serious inconsistency	serious[a]	very serious[b]	Folic acid also given	10/110 (9.1%)	4/53 (7.5%)	RR 1.2 (0.4 to 3.66)	15 more per 1000 (from 45 fewer to 201 more)	⊕OOO VERY LOW

(a) Data not given separately for the 2 placebo groups (subcutaneous and oral)
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) Ho study (19.2% weighted) had unclear allocation concealment
(d) Larger study (Saurat): data not given separately for the 2 placebo groups (subcutaneous and oral)
(e) Ho study (20.6% weighted) had unclear allocation concealment and a long follow-up (6 months)

10.1.1.2 Evidence statements

In people with psoriasis, incrementally dosed methotrexate was statistically significantly better than placebo for:

- Clear/nearly clear (PGA) at 16 weeks [1 study; 156 participants; moderate quality evidence][323]
- PASI75 at 4-6 months [2 studies; 192 participants; moderate quality evidence][323,324]
- PASI50 at 4-6 months [2 studies; 192 participants; moderate quality evidence][323,324]
- PASI change/final score at 4-6 months [2 studies; 192 participants; moderate quality evidence][323,324]

In people with psoriasis, there was no statistically significant difference between incrementally dosed methotrexate and placebo for:

- PASI90 at 16 weeks [1 study; 156 participants; very low quality evidence][323]
- Severe adverse events at 26 weeks [1 study; 163 participants; very low quality evidence][323]
- Withdrawal due to toxicity at 26 weeks [1 study; 159 participants; very low quality evidence][323]
- Raised liver enzymes at 26 weeks [1 study; 163 participants; very low quality evidence][323]

10.1.2 Methotrexate vs ciclosporin for induction of remission

Table 139: Evidence profile comparing methotrexate vs ciclosporin for induction of remission

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciclosporin	Methotrexate	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90) - Incremental dose MTX (7.5 up to 15 mg/wk) (follow-up 12 weeks)											
1 Flytstrom 2008	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	Folic acid also given	9/31 (29%)	4/37 (10.8%)	RR 2.69 (0.91 to 7.88)	183 more per 1000 (from 10 fewer to 744 more)	⊕⊕OO LOW
Clear/nearly clear (PASI90) - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 16 weeks)											
1 Heydendael 2003	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	14/42 (33.3%)	17/43 (39.5%)	RR 0.84 (0.48 to 1.48)	63 fewer per 1000 (from 206 fewer to 190 more)	⊕OOO VERY LOW
Clearance - High dose MTX (0.5 mg/kg/wk) (follow-up 10 weeks)											
1 Sandhu 2003	randomised trials	very serious[e]	no serious inconsistency	serious[f]	no serious imprecision	none	6/15 (40%)	13/15 (86.7%)	RR 0.46 (0.24 to 0.88)	468 fewer per 1000 (from 104 fewer to 659 fewer)	⊕OOO VERY LOW
Time-to-remission - PASI75 - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 16 weeks)											
1 Heydendael 2003	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	serious[b]	none	30/42 (71.4%)	26/43 (60.5%)	HR 1.63 (0.96 to 2.77)	175 more per 1000 (from 15 fewer to 319 more)	⊕⊕OO LOW
Time-to-remission – PASI90 - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 16 weeks)											
1 Heydendael 2003	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	14/42 (33.3%)	17/43 (39.5%)	HR 0.87 (0.43 to 1.76)	41 fewer per 1000 (from 201 fewer to 192 more)	⊕OOO VERY LOW
PASI75 - Incremental dose MTX (7.5 up to 15 mg/wk) (follow-up 12 weeks)											

1 Flytstrom 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	Folic acid also given	18/31 (58.1%)	9/37 (24.3%)	RR 2.39 (1.26 to 4.54)	338 more per 1000 (from 63 more to 861 more)	⊕⊕⊕O MODERATE
PASI75 - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 16 weeks)											
1 Heydendael 2003	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	serious[b]	none	30/42 (71.4%)	26/43 (60.5%)	RR 1.18 (0.87 to 1.61)	109 more per 1000 (from 79 fewer to 369 more)	⊕⊕OO LOW
PASI50 - Incremental dose MTX (7.5 up to 15 mg/wk) (follow-up 12 weeks)											
1 Flytstrom 2008	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	Folic acid also given	27/31 (87.1%)	24/37 (64.9%)	RR 1.34 (1.02 to 1.76)	221 more per 1000 (from 13 more to 493 more)	⊕⊕⊕O MODERATE
Final PASI - High dose MTX (0.5 mg/kg/wk) (follow-up 12 weeks; better indicated by lower values)											
1 Sandhu 2003	randomised trials	very serious[e]	no serious inconsistency	serious[f,h]	no serious imprecision	none	15	15	-	MD 3.9 higher (0.69 to 7.11 higher)	⊕OOO VERY LOW
Final PASI - incremental dose MTX (within licensed range; maximum 22.5 mg/wk) (follow-up 12-16 weeks; better indicated by lower values)											
2 Flytstrom 2008 Heydendael 2003	randomised trials	serious[i]	no serious inconsistency	serious[h]	no serious imprecision	none	73	80	-	MD 1.62 lower (2.7 lower to 0.54 lower)	⊕⊕OO LOW
Change in NAPSI – Decreasing MTX dose (15 mg/wk reduced to 10 mg/wk) (follow-up 6 months; better indicated by higher values)											
1 Gumusel 2011	randomised trials	serious[j]	no serious inconsistency	no serious indirectness	serious[b]	Folic acid also given	19	18	-	MD 4.8 higher (3.73 lower to 13.33 higher)	⊕⊕OO LOW
Elevated liver enzymes - MTX dose within licensed range (maximum 22.5 mg/wk) (follow-up 12-24 weeks)											
3 Flytstrom 2008 Heydendael 2003 Gumusel 2011	randomised trials	serious[i]	no serious inconsistency	no serious indirectness[k]	no serious imprecision	Folic acid also given in Flytstrom and Gumusel studies	0/92 (0%)	20/98 (20.4%)	RR 0.07 (0.01 to 0.38)	190 fewer per 1000 (from 127 fewer to 202 fewer)	⊕⊕⊕O MODERATE

Elevated creatinine - Standard MTX dose range (maximum 15 mg/wk) (follow-up 12-24 weeks)											
2 Flytstrom 2008 Gumusel 2011	randomised trials	serious[l]	no serious inconsistency	no serious indirectness[m]	no serious imprecision	Folic acid also given	8/50 (16%)	0/55 (0%)	RR 9.79 (1.32 to 72.65)	-	⊕⊕⊕O MODERATE
Hypertension requiring treatment - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 16 weeks)											
1 Heydendael 2003	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	2/42 (4.8%)	0/43 (0%)	RR 5.12 (0.25 to 103.5)	-	⊕OOO VERY LOW
Diastolic hypertension - High dose MTX (0.5 mg/kg/wk) (follow-up 12 weeks)											
1 Sandhu 2003	randomised trials	very serious[e]	no serious inconsistency	serious[f]	very serious[d]	none	4/15 (26.7%)	0/15 (0%)	RR 9 (0.53 to 153.79)	-	⊕OOO VERY LOW
Withdrawal due to toxicity - Standard MTX dose range (maximum 15 mg/wk) (follow-up 12-16 weeks)											
2 Flytstrom 2008 Gumusel 2011	randomised trials	serious[n]	no serious inconsistency	no serious indirectness	serious[b]	Folic acid also given	6/50 (12%)	1/55 (1.8%)	RR 4.6 (0.84 to 25.16)	65 more per 1000 (from 3 fewer to 439 more)	⊕⊕OO LOW
Withdrawal due to toxicity - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 16 weeks)											
1 Heydendael 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/42 (2.4%)	12/43 (27.9%)	RR 0.09 (0.01 to 0.63)	254 fewer per 1000 (from 103 fewer to 276 fewer)	⊕⊕⊕⊕ HIGH
Remaining clear at 12 weeks (after tapering high dose MTX (0.5 mg/kg/wk)) (follow-up 12 weeks)											
1 Sandhu 2003	randomised trials	very serious[e]	no serious inconsistency	serious[f]	serious[b]	none	2/6 (33.3%)	13/13 (100%)	RR 0.37 (0.14 to 1.01)	630 fewer per 1000 (from 860 fewer to 10 more)	⊕OOO VERY LOW
Mean change from baseline in DLQI - Incremental dose MTX (7.5 up to 15 mg/wk) (follow-up 8 weeks)											
1 Flytstrom 2008	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[o]	Folic acid also given	31	37	MTX: 42% CSA: 71% p=0.0078	-	⊕⊕OO LOW

Mean change from baseline in DLQI - Incremental dose MTX (7.5 up to 15 mg/wk) (follow-up 12 weeks)											
1 Flytstrom 2008	randomised trials	serious[a]	no serious inconsistency	serious[p]	serious[o]	Folic acid also given	31	37	NS difference		⊕OOO VERY LOW
Median time to relapse - Incremental dose MTX (15 up to 22.5 mg/wk) (follow-up 8 weeks)											
1 Heydendael 2003	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[o]	none	42	43	MTX: 4 weeks CSA: 4 weeks Note: NS difference in duration of PASI75 or PASI90 response (p = 0.43 and 0.34, respectively from log rank test)[p]	-	⊕⊕OO LOW

(a) High differential drop out before treatment began (MTX = 9.8%; CSA = 27.9%) but baseline characteristics still matched; and differential drop out during treatment due to adverse events: MTX = 0; CSA = 12.9%
(b) Confidence interval ranges from clinically important effect to no effect
(c) Differential drop out rate: MTX = 27.9%; CSA = (2.4%) due in abnormal LFTs with high dose MTX
(d) Confidence interval crosses the boundary for clinical significance in favour of both treatment, as well as line of no effect
(e) Unclear allocation concealment, blinding and drop out rates
(f) Methotrexate dosing not within current UK practice
(g) Differential drop out rate in Heydendael study MTX = 27.9%; CSA = (2.4%) due in abnormal LFTs with high dose MTX
(h) Surrogate outcome for change in PASI
(i) Flytstrom: High differential drop out before treatment began (MTX = 9.8%; CSA = 27.9%) but baseline characteristics still matched; and differential drop out during treatment due to adverse events: MTX = 0; CSA = 12.9%. Differential drop out rate in Heydendael study MTX = 27.9%; CSA = (2.4%) due in abnormal LFTs with high dose MTX
(j) Inadequate sequence generation and unclear blinding
(k) Unclear definition of elevation of LFTs in Heydendel paper

(l) 1/2 High differential drop out before treatment began (MTX = 9.8%; CSA = 27.9%) but baseline characteristics still matched; and differential drop out during treatment due to adverse events: MTX = 0; CSA = 12.9% 1/2 Inadequate sequence generation and unclear blinding
(m) Unclear definition of elevation
(n) 1/2 studies (69.2% weighted) inadequate sequence generation and unclear blinding
(o) No range available
(p) Only states non-significant - no data provided
(q) Hazard ratio could not be calculated as numbers relapsing not reported

Only ITT data were available for the Flytstrom and Heydendael studies, and the assumptions were not stated so it was not possible to use an available case analysis.

The dosing schedules were considered clinically similar enough to pool in the Flytstrom and Heydendael studies, but the Sandhu study was considered to be different. Therefore, data from Flytstrom and Heydendael were pooled unless there was significant heterogeneity.

10.1.211 Evidence statements

In people with psoriasis, ciclosporin was statistically significantly better than methotrexate for:

- PASI75 at 12 weeks (incremental MTX dose; 7.5 up to 15 mg/wk) [1 study; 68 participants; moderate quality evidence][325]
- PASI50 at 12 weeks (incremental MTX dose; 7.5 up to 15 mg/wk) [1 study; 68 participants; moderate quality evidence][325]
- Final PASI at 12-16 weeks (incremental dose MTX within licensed range; maximum 22.5 mg/wk) [2 studies; 153 participants; low quality evidence][325,326]
- Elevated liver enzymes at 12-24 weeks (MTX dose within licensed range; maximum 22.5 mg/wk) [3 studies; 190 participants; moderate quality evidence][325-327]
- Withdrawal due to toxicity at 16 weeks (incremental dose MTX; 15 up to 22.5 mg/wk) [1 study; 85 participants; high quality evidence][326]

In people with psoriasis, methotrexate was statistically significantly better than ciclosporin for:

- Final PASI at 12 weeks (high dose MTX; 0.5 mg/kg/wk) [1 study; 30 participants; very low quality evidence][328]
- Clearance at 10 weeks (high dose MTX; 0.5 mg/kg/wk) [1 study; 30 participants; very low quality evidence][328]
- Elevated creatinine at 12-24 weeks (standard MTX dose range; maximum 15 mg/wk) [2 studies; 105 participants; moderate quality evidence][325,327]

In people with psoriasis, there was no statistically significant difference between ciclosporin and methotrexate for:

- Clear/nearly clear (PASI90) at 12 weeks (incremental MTX dose; 7.5 up to 15 mg/wk) [1 study; 68 participants; low quality evidence][325]
- Clear/nearly clear (PASI90) at 16 weeks (incremental dose MTX; 15 up to 22.5 mg/wk) [1 study; 85 participants; very low quality evidence][326]
- Time-to-PASI75 (incremental dose MTX; 15 up to 22.5 mg/wk) after follow-up for a maximum of 16 weeks [1 study; 85 participants; low quality evidence][326]
- Time-to-PASI90 (incremental dose MTX; 15 up to 22.5 mg/wk) after follow-up for a maximum of 16 weeks [1 study; 85 participants; very low quality evidence][326]
- PASI75 at 16 weeks (incremental dose MTX; 15 up to 22.5 mg/wk) [1 study; 85 participants; low quality evidence][326]
- Remaining clear at 12 weeks (after tapering) [1 study; 19 participants; very low quality evidence][328]
- Change in NAPSI (decreasing MTX dose; 15 mg/wk reduced to 10 mg/wk) at 6 months [1 study; 37 participants; low quality evidence][327]
- Hypertension at 16 weeks (incremental dose MTX; 15 up to 22.5 mg/wk) [1 study; 85 participants; very low quality evidence][326]
- Hypertension at 12 weeks (high dose MTX; 0.5 mg/kg/wk) [1 study; 30 participants; very low quality evidence][328]
- Withdrawal due to toxicity at 12-16 weeks (standard MTX dose range; maximum 15 mg/wk) [2 studies; 105 participants; low quality evidence][325,327]

Evidence statements for individual studies where insufficient data were available to perform original statistical analysis comparing ciclosporin and methotrexate in people with psoriasis:

- Percentage change in DLQI from baseline to 12 weeks was statistically significantly better with ciclosporin than methotrexate (incremental dose; 7.5 up to 15 mg/wk) at 8 weeks [1 study; 68 participants; low quality evidence][325]
- There was no significant difference between ciclosporin and methotrexate (incremental dose; 7.5 up to 15 mg/wk) for change in DLQI from baseline to 12 weeks [1 study; 68 participants; very low quality evidence][325]
- There was no significant difference between ciclosporin and methotrexate (incremental dose; 15 up to 22.5 mg/wk) in median time to relapse after a maximum follow-up of 8 weeks post-treatment [1 study; 85 participants; low quality evidence][326]

10.1.202 Subgroups and heterogeneity

Heterogeneity was present for the outcomes of clear or nearly clear, PASI75, final PASI and withdrawal due to toxicity between three studies[325,326,328]. This was thought to be due to the different dosing regimens of methotrexate used in the included studies, as the estimate of efficacy moved towards favouring methotrexate compared with ciclosporin as the dose of methotrexate used increased (while the dose of ciclosporin was similar among the studies). Conversely, there were relatively more withdrawals due to toxicity with higher dose methotrexate compared with ciclosporin. However, it is also possible that the differences were caused or contributed to by the differences in the use of folic acid. The Flytstrom study[325], which also used the lowest dosing schedule, was the only one to have administered folic acid which may have reduced the efficacy of methotrexate while also making it more tolerable.

It was unclear why there was no heterogeneity between the Heydendael and Flytstrom studies for the outcome of final PASI in contrast to the outcome of PASI75. However, the final scores do mask a slightly greater difference in the change in PASI between the two studies owing to baseline differences, with the difference in change scores between the methotrexate and ciclosporin groups being greater in the Flytstrom study in which methotrexate showed lower efficacy than in the Heydendael study (the percentage change in PASI was greater in the ciclosporin group by 16.5% in the Flytstrom study but 10.2% in the Heydendael study).

10.1.13 Acitretin vs placebo for induction of remission

10.1.321 Evidence profile

3 **Table 140: Evidence profile comparing acitretin vs placebo for the induction of remission**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acitretin	Placebo	Relative (95% CI)	Absolute	
PASI75 (8 weeks) - 10 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	very serious[c]	none	8/25 (32%)	6/32 (18.8%)	RR 1.46 (0.6 to 3.54)	86 more per 1000 (from 75 fewer to 476 more)	⊕OOO VERY LOW
PASI75 (8 weeks) - 25 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	serious[d]	none	12/25 (48%)	6/32 (18.8%)	RR 2.13 (0.96 to 4.75)	212 more per 1000 (from 8 fewer to 703 more)	⊕OOO VERY LOW
PASI75 (8 weeks) - 50 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	no serious imprecision	none	16/31 (51.6%)	6/32 (18.8%)	RR 2.7 (1.26 to 5.81)	319 more per 1000 (from 49 more to 902 more)	⊕OOO VERY LOW
PASI75 (8 weeks) - 75 mg acitretin (follow-up 8 weeks)											
1 Goldfarb 1988	randomised trials	very serious[e]	no serious inconsistency	serious[6]	very serious[c]	none	2/5 (40%)	1/12 (8.3%)	RR 4.8 (0.55 to 41.7)	317 more per 1000 (from 37 fewer to 1000 more)	⊕OOO VERY LOW

Cheilitis (8 weeks) - 10 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[g]	no serious imprecision	none	17/23 (73.9%)	8/31 (25.8%)	RR 2.75 (1.39 to 5.44)	452 more per 1000 (from 101 more to 1000 more)	⊕OOO VERY LOW
Cheilitis (8 weeks) - 25 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[g]	no serious imprecision	none	18/22 (81.8%)	8/31 (25.8%)	RR 3.06 (1.66 to 5.66)	532 more per 1000 (from 170 more to 1000 more)	⊕OOO VERY LOW
Cheilitis (8 weeks) - 50 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[g]	no serious imprecision	none	27/29 (93.1%)	8/31 (25.8%)	RR 3.45 (1.92 to 6.2)	632 more per 1000 (from 237 more to 1000 more)	⊕OOO VERY LOW
Cheilitis (8 weeks) - 75 mg acitretin (follow-up 8 weeks)											
1 Goldfarb 1988	randomised trials	serious[e]	no serious inconsistency	serious[h]	serious[i]	none	4/5 (80%)	3/12 (25%)	RR 3.2 (1.09 to 9.36)	550 more per 1000 (from 23 more to 1000 more)	⊕OOO VERY LOW
Cheilitis (6 months) - 10 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	no serious imprecision	none	16/20 (80%)	6/20 (30%)	RR 2.67 (1.32 to 5.39)	501 more per 1000 (from 96 more to 1000 more)	⊕OOO VERY LOW
Cheilitis (6 months) - 25 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	no serious imprecision	none	17/20 (85%)	6/20 (30%)	RR 2.83 (1.42 to 5.67)	549 more per 1000 (from 126 more to 1000 more)	⊕OOO VERY LOW
Cheilitis (6 months) - 50 mg acitretin (follow-up 6 months)											
1	randomised	very	no serious	very serious[j]	no serious	none	19/20	6/20	RR 3.17 (1.61 to	651 more per 1000 (from 183	⊕OOO

Lassus 1988	trials	serious[e]	inconsistency		imprecision		(95%)	(30%)	6.23)	more to 1000 more)	VERY LOW
Hair loss (8 weeks) - 10 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[g]	very serious[c]	none	0/23 (0%)	1/31 (3.2%)	RR 0.72 (0.03 to 15.26)	9 fewer per 1000 (from 31 fewer to 460 more)	⊕OOO VERY LOW
Hair loss (8 weeks) - 25 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[g]	very serious[g]	none	1/22 (4.5%)	1/31 (3.2%)	RR 2.4 (0.18 to 31.29)	45 more per 1000 (from 26 fewer to 977 more)	⊕OOO VERY LOW
Hair loss (8 weeks) - 50 mg acitretin (follow-up 8 weeks)											
2 Lassus 1988 Goldfarb 1988	randomised trials	very serious[a]	no serious inconsistency	very serious[g]	no serious imprecision	none	8/29 (27.6%)	1/31 (3.2%)	RR 6.06 (1.13 to 32.6)	163 more per 1000 (from 4 more to 1000 more)	⊕OOO VERY LOW
Hair loss (8 weeks) - 75 mg acitretin (follow-up 8 weeks)											
1 Goldfarb 1988	randomised trials	very serious[e]	no serious inconsistency	serious[h]	very serious[h]	none	2/5 (40%)	1/12 (8.3%)	RR 4.8 (0.55 to 41.7)	317 more per 1000 (from 37 fewer to 1000 more)	⊕OOO VERY LOW
Hair loss (6 months) - 10 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	3/20 (15%)	2/20 (10%)	RR 1.5 (0.28 to 8.04)	50 more per 1000 (from 72 fewer to 704 more)	⊕OOO VERY LOW
Hair loss (6 months) - 25 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	3/20 (15%)	2/20 (10%)	RR 1.5 (0.28 to 8.04)	50 more per 1000 (from 72 fewer to 704 more)	⊕OOO VERY LOW
Hair loss (6 months) - 50 mg acitretin (follow-up 6 months)											

1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	no serious imprecision	none	15/20 (75%)	2/20 (10%)	RR 7.5 (1.97 to 28.61)	650 more per 1000 (from 97 more to 1000 more)	⊕OOO VERY LOW
Increased triglycerides (8 weeks) - 10 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/18 (11.1%)	1/19 (5.3%)	RR 2.11 (0.21 to 21.32)	58 more per 1000 (from 42 fewer to 1000 more)	⊕OOO VERY LOW
Increased triglycerides (8 weeks) - 25 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/17 (11.8%)	1/19 (5.3%)	RR 2.24 (0.22 to 22.51)	65 more per 1000 (from 41 fewer to 1000 more)	⊕OOO VERY LOW
Increased triglycerides (8 weeks) - 50 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/18 (11.1%)	1/19 (5.3%)	RR 2.11 (0.21 to 21.32)	58 more per 1000 (from 42 fewer to 1000 more)	⊕OOO VERY LOW
Increased triglycerides (6 months) - 10 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	1/16 (6.3%)	1/19 (5.3%)	RR 1.19 (0.08 to 17.51)	10 more per 1000 (from 48 fewer to 869 more)	⊕OOO VERY LOW
Increased triglycerides (6 months) - 25 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	1/15 (6.7%)	1/19 (5.3%)	RR 1.27 (0.09 to 18.62)	14 more per 1000 (from 48 fewer to 927 more)	⊕OOO VERY LOW
Increased triglycerides (6 months) - 50 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	0/15 (0%)	1/19 (5.3%)	RR 0.42 (0.02 to 9.55)	31 fewer per 1000 (from 52 fewer to 450 more)	⊕OOO VERY LOW
Increased liver enzymes (8 weeks) - 10 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/18 (11.1%)	0/19 (0%)	RR 5.26 (0.27 to 102.66)	-	⊕OOO VERY LOW

Increased liver enzymes (8 weeks) - 25 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	no serious imprecision	none	0/17 (0%)	0/19 (0%)	not pooled	not pooled	⊕OOO VERY LOW
Increased liver enzymes (8 weeks) - 50 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	no serious imprecision	none	0/18 (0%)	0/19 (0%)	not pooled	not pooled	⊕OOO VERY LOW
Increased liver enzymes (6 months) - 10 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	1/16 (6.3%)	0/19 (0%)	RR 3.53 (0.15 to 81.11)	-	⊕OOO VERY LOW
Increased liver enzymes (6 months) - 25 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	3/15 (20%)	0/19 (0%)	RR 8.75 (0.49 to 157.34)	-	⊕OOO VERY LOW
Increased liver enzymes (6 months) - 50 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/15 (13.3%)	0/19 (0%)	RR 6.25 (0.32 to 121.14)	-	⊕OOO VERY LOW
Increased cholesterol (8 weeks) - 10 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/18 (11.1%)	3/19 (15.8%)	RR 0.7 (0.13 to 3.73)	47 fewer per 1000 (from 137 fewer to 431 more)	⊕OOO VERY LOW
Increased cholesterol (8 weeks) - 25 mg acitretin (follow-up 8 weeks)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	5/17 (29.4%)	3/19 (15.8%)	RR 1.86 (0.52 to 6.65)	136 more per 1000 (from 76 fewer to 892 more)	⊕OOO VERY LOW
Increased cholesterol (8 weeks) - 50 mg acitretin (follow-up 8 weeks)											
1	randomised	very	no serious	very serious[j]	very serious[c]	none	3/18	3/19	RR 1.06 (0.24 to	9 more per 1000 (from 120 fewer	⊕OOO

Lassus 1988	trials	serious[e]	inconsistency				(16.7%)	(15.8%)	4.57)	to 564 more)	VERY LOW
Increased cholesterol (6 months) - 10 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	2/16 (12.5%)	1/19 (5.3%)	RR 2.38 (0.24 to 23.84)	73 more per 1000 (from 40 fewer to 1000 more)	⊕OOO VERY LOW
Increased cholesterol (6 months) - 25 mg acitretin (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	0/15 (0%)	1/19 (5.3%)	RR 0.42 (0.02 to 9.55)	31 fewer per 1000 (from 52 fewer to 450 more)	⊕OOO VERY LOW
Withdrawal due to toxicity (all doses) (follow-up 6 months)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	very serious[c]	none	1/57 (1.8%)	0/19 (0%)	RR 1.03 (0.04 to 24.38)	-	⊕OOO VERY LOW
Improvement in sign scores (follow-up 8 weeks; Better indicated by higher values)											
1 Kingston 1987	randomised trials	very serious[k]	no serious inconsistency	very serious[l]	serious[m]	none	10	11	50 or 75 mg/day showed significant improvement on every parameter (scaling, erythema, thickness and pustulation), whereas those receiving 0 or 10 mg/day did not Most patients needed daily doses ≥0.66 mg/kg to initiate remission		⊕OOO VERY LOW
Final PASI (maintenance phase) (follow-up 6 months; Better indicated by lower values)											
1 Lassus 1988	observational studies[n]	very serious[j]	no serious inconsistency	no serious indirectness	serious[m]	none	10, 25 or 50 mg 60	20	No significant difference in PASI score between the placebo, 10, 25 and 50 mg groups		⊕OOO VERY LOW
Change in PASI (follow-up 8 weeks; Better indicated by higher values)											
1 Lassus 1988	randomised trials	very serious[e]	no serious inconsistency	very serious[j]	serious[o]	none	25 or 50 mg 40	40	Significantly greater reduction in PASI on 25 and 50 mg/day compared with placebo ($p<0.05$) No significant difference between 25 and 50 mg The mean percentage decrease in PASI score in the 10 mg group was greater than in the placebo group,		⊕OOO VERY LOW

									but did not differ significantly from any other group	
Adverse events (follow-up 6 months; Better indicated by lower values)										
1 Kingston 1987	observational studies[n]	very serious[k]	no serious inconsistency	serious[p]	serious[o]	dose response gradient[q]	21		More side effects at higher doses %of those receiving ≥0.66 mg/kg with: Cheilitis & mucosal dryness: 89 % Palmoplantar peeling: 86% Alopecia : 58%	⊕OOO VERY LOW

(a) 2/2 unclear allocation concealment and blinding not explained fully
(b) Unclear reporting of baseline characteristics and in Lassus trial steroids administered on request (numbers using differed between the groups); Goldfarb data is surrogate outcome measure of >75% global improvement
(c) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(d) Confidence interval ranges from clinically important effect to no effect
(e) Unclear allocation concealment and blinding not explained fully
(f) Unclear reporting of baseline characteristics and data are surrogate outcome measure of >75% global improvement
(g) Unclear reporting of baseline characteristics and in Lassus trial steroids administered on request (numbers using differed between the groups)
(h) Unclear reporting of baseline characteristics
(i) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important harm to no clinically important harm)
(j) Disease severity at baseline not reported and steroids administered on request (numbers using differed between the groups)
(k) Unclear baseline characteristics; high drop-out rate (38.1%) and numbers in each arm not given
(l) Surrogate outcome for change in PASI and placebo and 10 mg group combined
(m) No numerical data
(n) Open extension phase of RCT with dose adjustment
(o) Insufficient information to analyse precision
(p) Surrogate outcome measure for serious adverse events
(q) There were more side effects at higher doses

10.1.312 Evidence statements

In people with psoriasis, acitretin was statistically significantly better than placebo for:

- PASI75 (50 mg acitretin) at 8 weeks [2 studies; 63 participants; very low quality evidence][329,330]

In people with psoriasis, acitretin was statistically significantly more likely than placebo to result in:

- Cheilitis at 8 weeks (10, 25 and 50 mg acitretin) [2 studies; 54, 53 and 60 participants, respectively; very low quality evidence][329,330]
- Cheilitis at 8 weeks (75 mg acitretin) [1 study; 17 participants; very low quality evidence][330]
- Cheilitis at 6 months (10, 25 and 50 mg acitretin) [1 study; 40 participants; very low quality evidence][329]
- Hair loss at 8 weeks (50 mg acitretin) [2 studies; 60 participants; very low quality evidence][329,330]
- Hair loss at 6 months (50 mg acitretin) [1 study; 40 participants; very low quality evidence][329]

In people with psoriasis, there was no statistically significant difference between acitretin and placebo for:

- PASI75 at 8 weeks (10 and 25 mg acitretin) [2 studies; 57 participants; very low quality evidence][329,330]
- PASI75 at 8 weeks (75 mg acitretin) [1 study; 17 participants; very low quality evidence][330]
- Withdrawal due to toxicity at 8 weeks [1 study; 76 participants; very low quality evidence][329]
- Hair loss at 8 weeks (10 and 25 mg acitretin) [2 studies; 54 and 53 participants, respectively; very low quality evidence] [329,330]
- Hair loss at 8 weeks (75 mg acitretin) [1 study; 17 participants; very low quality evidence][330]
- Hair loss at 6 months (10 and 25 mg acitretin) [1 study; 40 participants; very low quality evidence][329]
- Increased triglycerides at 8 weeks (10, 25 and 50 mg acitretin) [1 study; 37, 36 and 37 participants, respectively; very low quality evidence][329]
- Increased triglycerides at 6 months (10, 25 and 50 mg acitretin) [1 study; 35, 34 and 34 participants, respectively; very low quality evidence][329]
- Increased liver enzymes at 8 weeks (10 mg acitretin) [1 study; 37 participants; very low quality evidence][329]
- Increased liver enzymes at 6 months (10, 25 and 50 mg acitretin) [1 study; 35, 34 and 34 participants, respectively; very low quality evidence][329]
- Increased cholesterol at 8 weeks (10, 25 and 50 mg acitretin) [1 study; 37, 36 and 37 participants, respectively; very low quality evidence][329]
- Increased cholesterol at 6 months (10 and 25 mg acitretin) [1 study; 35 participants; very low quality evidence][329]

In people with psoriasis there were no events with either acitretin or placebo for:

- Increased liver enzymes at 8 weeks (25 and 50 mg acitretin) [1 study; 37 participants; very low quality evidence][329]

Evidence statements for individual studies where insufficient data were available to perform original statistical analysis comparing acitretin and placebo in people with psoriasis:

- Acitretin 50 or 75 mg was better than placebo or 10 mg acitretin for improvement in scaling, erythema, thickness and pustulation at 8 weeks [1 study; 21 participants; very low quality evidence][331]

- Reduction in PASI at 8 weeks was significantly greater in the groups receiving 25 mg/day and 50 mg/day compared with placebo, but there was no significant difference between the 25 and 50 mg groups. Additionally, the mean percentage decrease in PASI score in the 10 mg group was greater than in the placebo group, but did not differ significantly from 25 or 50 mg groups [1 study; 80 participants; very low quality evidence][329]
- There was no significant difference in PASI score at 6 months between the placebo, 10, 25 and 50 mg groups at 6 months [1 study; 80 participants; very low quality evidence][329]
- There were more side effects at higher doses of acitretin at 6 months [1 study; 21 participants; very low quality evidence][331]

10.1.303 Subgroups and heterogeneity

For the outcomes of PASI75, hair loss and cheilitis from two studies[329,330] there was no statistically significant difference between the dose subgroups, suggesting that the increase in efficacy and toxicity is negligible. However, the small size of the studies and wide confidence intervals may mean that the true difference in effect has not been detected, although the point estimates did increase in favour of acitretin for efficacy and in favour of placebo for toxicity as the dose increased.

10.1.14 Increasing vs decreasing acitretin dosing schedule for induction of remission

10.1.14.1 Evidence profile

Table 141: Evidence profile comparing increasing vs decreasing acitretin dosing schedule for induction of remission

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Decreasing acitretin dosing schedule	Increasing acitretin dosing schedule	Relative (95% CI)	Absolute	
% change in PASI (follow-up 6 weeks; better indicated by higher values)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	none	19	21	-	MD 6.8 higher (Decreasing: 67.1% Increasing: 62.7%)	⊕OOO VERY LOW
Cheilitis (follow-up 6 weeks)											
1 Berbis, 1989	randomised trials	serious a	no serious inconsistency	serious[b]	no serious imprecision	none	21/21 (100%)	21/21 (100%)	RR 1 (0.91 to 1.09)	0 fewer per 1000 (from 90 fewer to 90 more)	⊕⊕OO LOW
Hair loss (follow-up 6 weeks)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[d]	none	6/21 (28.6%)	1/21 (4.8%)	RR 6 (0.79 to 45.63)	238 more per 1000 (from 10 fewer to 2125 more)	⊕OOO VERY LOW
Withdrawal due to toxicity (follow-up 6 weeks)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	very serious[e]	none	2/21 (9.5%)	0/20 (0%)	RR 4.77 (0.24 to 93.67)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW

Quality assessment							Summary of findings				
Serious adverse events (follow-up 6 weeks; better indicated by lower values)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[f]	serious[g]	none	20	19	-	See Table 142	⊕OOO VERY LOW

(a) Unclear allocation concealment
(b) Higher proportion of men in group 1 and more with pustular and guttate psoriasis in group 3
(c) No SD provided
(d) Confidence interval ranges from clinically important effect to no effect
(e) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(f) Analysing different doses within each randomised group (not the randomised comparison)
(g) Insufficient data to analyse precision

10.1.412 Evidence statements

In people with psoriasis, there was no statistically significant difference between acitretin increasing and decreasing doses for:

- Cheilitis at 6 weeks [1 study; 42 participants; low quality evidence][332]
- Hair loss at 6 weeks [1 study; 42 participants; very low quality evidence][332]
- Withdrawal due to toxicity at 6 weeks [1 study; 41 participants; very low quality evidence][332]

Table 142: Summary of non-analysed data for increasing vs decreasing acitretin dosing

Study	Total N	Follow-up	Result					Treatment favoured
Severe clinical adverse reactions								
Berbis	42	6 weeks	**Treatment period**	**Increasing dose** Dose (mg/d)	N'/n	**Decreasing dose** Dose (mg/d)	N'/n	Low dose
			Week 0-2*	10	0/21	50	9/21	
			Week 3-4	30	3/20	30	5/20	
			Week 5-6**	50	8/20	10	2/19	
			*Increasing vs decreasing: p<0.01					
			**Increasing vs decreasing: p =0.06					

Evidence statements for individual studies where insufficient data were available to perform original statistical analysis comparing increasing and decreasing acitretin dosing in people with psoriasis:

- Decreasing acitretin was slightly better than increasing doses for percentage change in PASI at 6 weeks [1 study; 40 participants; very low quality evidence][332]. However, there was no statistically significant difference between the three treatment groups (increasing, decreasing and constant dosing) for percentage improvement in PASI (p=0.42).
- The severe adverse reactions at 6 weeks were dose dependent: their frequency and intensity increased progressively with increasing dose and decreased with decreasing dose.
    - o There were statistically significantly more adverse events for patients using 50 vs 10 mg acitretin [1 study; 42 participants; very low quality evidence] [332]

10.1.15 Increasing vs constant acitretin dosing schedule for induction of remission

10.1.15.1 Evidence profile

Table 143: Evidence profile comparing increasing vs constant acitretin dosing schedule for induction of remission

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Constant acitretin dosing schedule	Increasing acitretin dosing schedule	Relative (95% CI)	Absolute	
% change in PASI (6 weeks) (follow-up 6 weeks; better indicated by higher values)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[c]	none	19	21	-	MD 6.8 lower (Constant 55.9% Increasing: 62.7%)	⊕OOO VERY LOW
Cheilitis (follow-up 6 weeks)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	23/23 (100%)	21/21 (100%)	RR 1 (0.92 to 1.09)	0 fewer per 1000 (from 80 fewer to 90 more)	⊕⊕OO LOW
Hair loss (follow-up 6 weeks)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	very serious[d]	none	2/23 (8.7%)	1/21 (4.8%)	RR 1.83 (0.18 to 18.7)	40 more per 1000 (from 39 fewer to 843 more)	⊕OOO VERY LOW
Withdrawal due to toxicity (follow-up 6 weeks)											
1 Berbis, 1989	randomised trials	serious[a]	no serious inconsistency	serious[b]	very serious[d]	none	3/22 (13.6%)	0/20 (0%)	RR 6.39 (0.35 to 116.57)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW

(a) Unclear allocation concealment

1 *(b) Higher proportion of men in group 1 and more with pustular and guttate psoriasis in group 3*
2 *(c) No SD provided*
3 *(d) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect*

10.1.512 Evidence statements

In people with psoriasis, there was no statistically significant difference between acitretin increasing and constant doses for:

- Cheilitis at 6 weeks [1 study; 44 participants; low quality evidence][332]
- Hair loss at 6 weeks [1 study; 44 participants; very low quality evidence][332]
- Withdrawal due to toxicity at 6 weeks [1 study; 42 participants; very low quality evidence][332]

Evidence statements for individual studies where insufficient data were available to perform original statistical analysis comparing increasing and constant acitretin dosing in people with psoriasis:

- Increasing acitretin was slightly better than constant dosing for percentage change in PASI at 6 weeks [1 study; 40 participants; very low quality evidence][332]. However, there was no statistically significant difference between the three treatment groups (increasing, decreasing and constant dosing) for percentage improvement in PASI (p=0.42).

10.1.6 Ciclosporin vs placebo for induction of remission

10.1.6.1 Evidence profile

Table 144: Evidence profile for ciclosporin vs placebo for induction of remission

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciclosporin	Placebo	Relative (95% CI)	Absolute	
Clear/nearly clear on PGA - CSA 3 mg/kg/day (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/25 (36%)	0/25 (0%)	RR 19.00 (1.17 to 309.77)	-	⊕⊕⊕O MODERATE
Clear/nearly clear on PGA - CSA 5 mg/kg/day (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/20 (65%)	0/25 (0%)	RR 33.43 (2.11 to 530)	-	⊕⊕⊕O MODERATE
Clear/nearly clear on PGA - 7.5 mg/kg/day (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/15 (80%)	0/25 (0%)	RR 40.63 (2.58 to 640.1)	-	⊕⊕⊕O MODERATE
Clearance - CSA 14 mg/kg/day (follow-up 4 weeks)											
1 Ellis 1986	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/11 (18.2%)	0/10 (0%)	RR 4.58 (0.25 to 85.33)	-	⊕OOO VERY LOW
PASI 75 - CSA 1.25 mg/kg/day (follow-up 10 weeks)											
1 Meffert 1997	randomised trials	serious[c]	no serious inconsistency	no serious indirectness[d]	very serious[b]	none	4/41 (9.8%)	2/43 (4.7%)	RR 2.1 (0.41 to 10.84)	51 more per 1000 (from 27 fewer to 458 more)	⊕OOO VERY LOW
PASI 75 - CSA 2.5-3.0 mg/kg/day (follow-up 8-10 weeks)											

2 Meffert 1997 Ellis 1991	randomised trials	serious[e]	no serious inconsistency	no serious indirectness[d]	no serious imprecision	none	16/69 (23.2%)	3/68 (4.4%)	RR 6.24 (1.94 to 20.11)	231 more per 1000 (from 41 more to 843 more)	⊕⊕⊕O MODERATE
PASI 75 - CSA 5 mg/kg/day (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness[d]	no serious imprecision	none	12/20 (60%)	1/25 (4%)	RR 15.00 (2.13 to 105.79)	560 more per 1000 (from 45 more to 1000 more)	⊕⊕⊕O MODERATE
PASI 50 CSA 2.5-7 mg/kg/day (follow-up 4-10 weeks)											
2 Guenther 1991 van Joost 1988	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/22 (90.9%)	1/21 (4.8%)	RR 12.97 (2.77 to 60.81)	570 more per 1000 (from 84 more to 1000 more)	⊕⊕OO LOW
Mean % change in PASI - CSA 2.5 mg/kg/day (follow-up 10 weeks; Better indicated by higher values)											
1 Meffert 1997	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	39	-	MD 45.1 higher (30.34 to 59.86 higher)	⊕⊕⊕O MODERATE
Mean % change in PASI - CSA 1.25 mg/kg/day (follow-up 10 weeks; Better indicated by higher values)											
1 Meffert 1997	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	39	-	MD 21.3 higher (5.7 to 36.9 higher)	⊕⊕⊕O MODERATE
Hypertension CSA 2.5-14 mg/kg/day (follow-up 8-10 weeks)											
2 Guenther 1991 Ellis 1986	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	very serious[b]	none	9/23 (39.1%)	7/21 (33.3%)	RR 1.15 (0.61 to 2.17)	50 more per 1000 (from 130 fewer to 390 more)	⊕OOO VERY LOW
Decreased GFR - CSA 3 mg/kg (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	4/12 (33.3%)	0/9 (0%)	RR 6.92 (0.42 to 114.19)	-	⊕OOO VERY LOW
Decreased GFR - CSA 5 mg/kg (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	5/10 (50%)	0/9 (0%)	RR 10 (0.63 to 158.87)	-	⊕OOO VERY LOW

Decreased GFR - CSA 7.5 mg/kg (follow-up 8 weeks)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[h]	none	9/12 (75%)	0/9 (0%)	RR 14.62 (0.96 to 222.24)	-	⊕⊕OO LOW
Withdrawal due to toxicity CSA 5-14 mg/kg/day (follow-up 4 weeks)											
2 Ellis 1986 van Joost 1988	randomised trials	serious[i]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/21 (0%)	0/20 (0%)	-	-	⊕⊕⊕O MODERATE
Change in PASI CSA 3.0-7.5 mg/kg/day (follow-up 8 weeks; Better indicated by lower values)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[j]	none	60	25	-	PASI improved significantly in all groups receiving CSA compared to placebo (P<0.001 for each),	⊕⊕OO LOW
Change in PASI CSA 3.0-7.5 mg/kg/day (follow-up 8 weeks; Better indicated by lower values)											
1 Ellis 1991	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[j]	none	60	25	-	NS difference in PASI score between 5 and 7 mg/kg (P>0.4), but each better than the response in the group receiving the lowest dose (P<0.01 for each comparison).	⊕⊕OO LOW

(a) Unclear allocation concealment
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) Unclear method of randomisation and allocation concealment
(d) These data were derived from a published review
(e) 2/2 unclear allocation concealment; 1/2 unclear method of randomisation
(f) Unclear allocation concealment in 2/2 studies; 1/2 high differential dropout in placebo group (8/11 withdrawn due to treatment failure by week 6)
(g) Unclear method of randomisation and allocation concealment in 2/2 studies
(h) Confidence interval ranges from clinically important effect to no effect
(i) 2/2 unclear allocation concealment
(j) Insufficient data to analyse precision

10.1.612 Evidence statements

In people with psoriasis, ciclosporin administered for induction of remission was statistically significantly better than placebo for:

- Clear/nearly clear on PGA at 8 weeks (3, 5 or 7.5 mg/kg/day) [1 study; 50, 45 and 40 participants, respectively; moderate quality evidence][333]
- PASI75 at 8-10 weeks (2.5-3.0 or 5 mg/kg) [2 studies; 157 participants; moderate quality evidence][333,334]
- PASI50 at 4-10 weeks [2 studies; 43 participants; low quality evidence][335,336]
- Mean % change in PASI (1.25 and 2.5 mg/kg/day CSA) [1 study; 79 and 80 participants; moderate quality evidence][334]

In people with psoriasis, there was no statistically significant difference between ciclosporin and placebo for:

- Clearance at 4 weeks (14 mg/kg/day) [1 study; 21 participants; very low quality evidence][337]
- PASI75 at 10 weeks (1.25 mg/kg) [1 study; 84 participants; very low quality evidence][334]
- Hypertension at 8-10 weeks [2 studies; 44 participants; very low quality evidence][335,337]
- Decreased glomerular filtration rate at 8 weeks (3, 5 and 7.5 mg/kg/day) [1 study; 21, 19 and 21 participants, respectively; low to very low quality evidence][333]

There were no events with either ciclosporin or placebo for:

- Withdrawal due to toxicity at 4 weeks [2 studies; 41 participants; moderate quality evidence][336,337]

Evidence statements for individual studies where no numerical analyses could be performed due to insufficient information comparing ciclosporin and placebo in people with psoriasis:

- Ciclosporin (3.0, 5.0 or 7.5 mg/kg/day) administered for induction of remission was statistically significantly better than placebo for improvement in PASI at 8 weeks [1 study; 85 participants; low quality evidence][333]
- Ciclosporin (5.0 or 7.5 mg/kg/day) administered for induction of remission is statistically significantly better than ciclosporin (3.0 mg/kg/day) for improvement in PASI at 8 weeks, but there was no significant difference between 5 and 7.5 mg/kg/day [1 study; 85 participants; low quality evidence][333]

10.1.623 Subgroups and heterogeneity

For the outcomes of clear/nearly clear on PGA, PASI75 and decrease in glomerular filtration rate from two studies[333,334] there was no statistically significant subgroup differences between the ciclosporin doses (3, 5 and 7.5 mg/kg/day in one study[333] and 1.25 or 2.5 mg/kg/day in the other[334]), suggesting that the increase in efficacy and toxicity is negligible. However, the small size of the studies and wide confidence intervals may mean that the true difference in effect has not been detected, although the point estimates did increase in favour of ciclosporin for efficacy and in favour of placebo for toxicity as the dose increased.

For the outcome of percentage change in PASI there was a statistically significant difference between the 1.25 and 2.5 mg/kg/day dose subgroups from one study[334]. The percentage change was significantly greater compared with placebo in the higher dose group.

10.1.7 Ciclosporin dosage comparisons for induction of remission

10.1.7.1 Evidence profile

Table 145: Evidence profile for ciclosporin dosage comparison for induction of remission

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ciclosporin low dose	Ciclosporin high dose	Relative (95% CI)	Absolute	
PASI 75 – initial CSA dose 1.25 vs 2.5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	randomised trials	very serious[a]	no serious inconsistency	very serious[b]	serious[c]	none	68/109 (62.4%)	78/108 (72.2%)	RR 0.86 (0.72 to 1.04)	101 fewer per 1000 (from 202 fewer to 22 more)	⊕OOO VERY LOW
PASI 75 - CSA 2.5 vs 5.0 mg/kg (follow-up 12 weeks)											
1 Laburte, 1994	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	57/119 (47.9%)	117/132 (88.6%)	RR 0.54 (0.44 to 0.66)	408 fewer per 1000 (from 301 fewer to 496 fewer)	⊕OOO VERY LOW
Elevated creatinine - CSA 1.25 mg/kg vs CSA 2.5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies[f]	serious[d]	no serious inconsistency	no serious indirectness	very serious5	none	1/109 (0.9%)	9/183 (4.9%)	RR 0.19 (0.02 to 1.45)	40 fewer per 1000 (from 48 fewer to 22 more)	⊕OOO VERY LOW
Elevated creatinine - CSA 2.5 mg/kg vs CSA 5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies	serious[d]	no serious inconsistency	no serious indirectness	serious [f]	none	9/183 (4.9%)	8/60 (13.3%)	RR 0.37 (0.15 to 0.91)	84 fewer per 1000 (from 12	⊕OOO VERY LOW

Quality assessment							Summary of findings				
										fewer to 113 fewer)	
Hypertension - CSA 1.25 mg/kg vs CSA 2.5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies[f]	serious4	no serious inconsistency	no serious indirectness	serious [f]	none	12/109 (11%)	38/183 (20.8%)	RR 0.53 (0.29 to 0.97)	98 fewer per 1000 (from 6 fewer to 147 fewer)	⊕OOO VERY LOW
Hypertension - CSA 2.5 mg/kg vs CSA 5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies[f]	serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	38/183 (20.8%)	16/60 (26.7%)	RR 0.78 (0.47 to 1.29)	59 fewer per 1000 (from 141 fewer to 77 more)	⊕OOO VERY LOW
Elevated uric acid (>400 micromol/L) - CSA 1.25 mg/kg vs CSA 2.5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies[f]	serious[d]	no serious inconsistency	no serious indirectness	serious[c]	none	21/109 (19.3%)	51/183 (27.9%)	RR 0.69 (0.44 to 1.08)	86 fewer per 1000 (from 156 fewer to 22 more)	⊕OOO VERY LOW
Elevated uric acid (>400 micromol/L) - CSA 2.5 mg/kg vs CSA 5 mg/kg (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies[f]	serious[d]	no serious inconsistency	no serious indirectness	serious [f]	none	51/183 (27.9%)	26/60 (43.3%)	RR 0.64 (0.44 to 0.93)	156 fewer per 1000 (from 30 fewer to 243 fewer)	⊕OOO VERY LOW
PASI75 (dose increases) (follow-up 12-36 weeks)											
1 Christophers, 1992	observational studies[f]	serious[d]	no serious inconsistency	no serious indirectness	serious[h]	dose response gradient[i]	109		See Table 146	-	⊕OOO VERY LOW

(a) Unclear allocation concealment, unblinded and unclear dropout rate
(b) Patients did not receive the randomised dose for the full induction period
(c) Confidence interval ranges from clinically important effect to no effect
(d) Unclear drop-out rates and outcomes reported as percentages but the denominators were sometimes unclear due to patients moving between dosage groups

1 *(e) Confidence interval crosses the boundary for clinical significance in favour of both treatment, as well as line of no effect*
2 *(f) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important harm to no clinically important harm)*
3 *(g) Non-randomised comparison within RCT*
4 *(h) Not analysed in MA because non-randomised comparison*
5 *(i) Increasing dose increased the chance of PASI75*
6

10.1.712 Evidence statements

In people with psoriasis, 5.0 mg/kg ciclosporin was statistically significantly better than 2.5 mg/kg ciclosporin administered for induction of remission for:

- PASI75 at 12 weeks [1 study; 251 participants; very low quality evidence][338]

In people with psoriasis, 5.0 mg/kg ciclosporin was statistically significantly more likely than 2.5 mg/kg ciclosporin administered for induction of remission to result in:

- Elevated creatinine at 12-36 weeks [1 study; 243 participants; very low quality evidence][339]
- Elevated uric acid at 12-36 weeks [1 study; 243 participants; very low quality evidence][339]

In people with psoriasis, 2.5 mg/kg ciclosporin was statistically significantly more likely than 1.25 mg/kg ciclosporin administered for induction of remission to result in:

- Hypertension at 12-36 weeks [1 study; 292 participants; very low quality evidence][339]

In people with psoriasis, there was no statistically significant difference between an initial dose of 1.25 and 2.5 mg/kg ciclosporin administered for induction of remission for:

- PASI75 at 12-36 weeks [1 study; 217 participants; very low quality evidence][339]
- Elevated creatinine at 12-36 weeks [1 study; 292 participants; very low quality evidence][339]
- Elevated uric acid at 12-36 weeks [1 study; 292 participants; very low quality evidence][339]

In people with psoriasis, there was no statistically significant difference between 2.5 and 5.0 mg/kg ciclosporin administered for induction of remission for:

- Hypertension at 12-36 weeks [1 study; 243 participants; very low quality evidence][339]

Table 146: Summary of non-analysed data for ciclosporin dosing increments for induction

Study	Total N	Follow-up	Result		
PASI75					
Christophers 1992	109	12-36 weeks	**Initial dose 1.25mg/kg/day**		
			Remission on to 1.25mg/kg/day	Remission after increased 2.5mg/kg/day	Remission after increased again to 5mg/kg/day
			19/109 (17.4%)	27/90 (30.0%)	22/63 (34.9%)
	108	12-36 weeks	**Initial dose 2.5mg/kg/day**		
			Remission on 2.5mg/kg/day	Remission after increased to 5mg/kg/day	
			60/108 (55.6%)	18/48 (37.5%)	

Evidence statements for non-randomised data comparing ciclosporin doses for induction of remission:

- In people with psoriasis, increasing the dose of ciclosporin allowed the achievement of PASI75 when lower doses were ineffective after 12-36 weeks [1 study; 109 participants; very low quality evidence][339]

10.1.8 Ciclosporin vs placebo for maintenance of remission

There were four studies[340-343] that addressed the use of ciclosporin for the maintenance of remission in psoriasis; therefore, all had an initial induction period and only those who responded were randomised to the maintenance phase. The Ellis study[343] defined remission as achieving clear or

nearly clear status on ciclosporin induction therapy and followed up for a further 4 months with low-dose ciclosporin (1.5 or 3 mg/kg/day) or placebo for 4 months. The Shupack study[342] defined remission as 70% improvement in BSA maintained for 2 weeks during a 16-week induction phase with 5.0 mg/kg/day ciclosporin, and the maintenance treatments were placebo or ciclosporin 3.0 mg/kg/day for 24 weeks. The Colombo study[340] defined remission as PASI75 during an 8-16-week induction period with any dose of ciclosporin and the maintenance dose was 5 mg/kg/day ciclosporin or placebo just on two consecutive days per week. The Thaci study[341] had an induction period where participants received either 200 mg/day or 2.5 mg/kg/day increased stepwise by 50 mg if response was insufficient and only those who achieved PASI75 by week 12 were randomised to the maintenance phase to receive either the last effective dose of ciclosporin 3-times a week or placebo for a further 12 weeks. The dosing regimens in the latter two studies were not considered similar enough to the former two studies for pooling to be appropriate.

10.1.8.1 Evidence profile

Table 147: Evidence profile comparing ciclosporin vs placebo for maintenance of remission

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciclosporin	Placebo	Relative (95% CI)	Absolute	
PASI 75 – CSA 5 mg/kg/day at weekends only (follow-up 24 weeks)											
1 Colombo 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	85/127 (66.9%)	33/62 (53.2%)	RR 1.26 (0.97 to 1.64)	138 more per 1000 (from 16 fewer to 341 more)	⊕OOO VERY LOW
Mean final PASI – CSA 5 mg/kg/day at weekends only (follow-up 24 weeks; better indicated by lower values)											
1 Colombo 2010	randomised trials	very serious[a]	no serious inconsistency	serious[c]	no serious imprecision	none	127	62	-	MD 1.5 lower (4.14 lower to 1.14 higher)	⊕OOO VERY LOW
Maintaining at least mild psoriasis following PASI75 – CSA three-times weekly (follow-up 12 weeks)											
1 Thaci 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[b]	none	14/31 (45.2%)	5/22 (22.7%)	RR 1.99 (0.84 to 4.71)	225 more per 1000 (from 36 fewer to 843 more)	⊕⊕OO LOW
Time-to-relapse – CSA three-times weekly (follow-up 12 weeks)											
1 Thaci 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/42 (40.5%)	29/51 (56.9%)	HR 0.45 (0.24 to 0.82)	254 fewer per 1000 (from 70 fewer to 386 fewer)	⊕⊕⊕O MODERATE
Time-to-relapse – CSA 3 mg/kg/day (follow-up 24 weeks)											
1 Shupack 1997	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	**Median time** CSA 3mg/kg/day: >24 weeks Placebo or CSA 1.5mg/kg/day: 6 weeks	35/83 (42.2%)	40/48 (83.3%)	HR 0.30 (0.19 to 0.49)	418 fewer per 1000 (from 249 fewer to 545 fewer)	⊕⊕⊕O MODERATE

Mean time to relapse (weeks) - CSA 1.5 mg/kg/day (follow-up up to 4 months; better indicated by higher values)											
1 Ellis 1995	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	20	20	-	MD 2 higher (0.77 lower to 4.77 higher)	⊕⊕OO LOW
Relapse rate - CSA 1.5 mg/kg/day (follow-up up to 4 months)											
1 Ellis 1995	randomised trials	serious[a]	no serious inconsistency	serious[e]	serious[b]	none	14/20 (70%)	18/20 (90%)	RR 0.78 (0.56 to 1.07)	198 fewer per 1000 (from 396 fewer to 63 more)	⊕OOO VERY LOW
Mean time to relapse (weeks) - CSA 3 mg/kg/day (follow-up up to 4 months; better indicated by higher values)											
1 Ellis 1995	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	20	-	MD 5 higher (2.23 to 7.77 higher)	⊕⊕⊕O MODERATE
Relapse rate - CSA 3 mg/kg/day (follow-up up to 4 months)											
1 Ellis 1995	randomised trials	serious[a]	no serious inconsistency	serious[e]	no serious imprecision	none	8/21 (38.1%)	18/20 (90%)	RR 0.42 (0.24 to 0.74)	522 fewer per 1000 (from 234 fewer to 684 fewer)	⊕⊕OO LOW
Relapse rate – CSA 5 mg/kg/day at weekends only (follow-up up to 24 weeks)											
1 Colombo 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	42/127 (33.1%)	29/62 (46.8%)	RR 0.71 (0.49 to 1.02)	136 fewer per 1000 (from 239 fewer to 9 more)	⊕OOO VERY LOW
Withdrawal due to toxicity (follow-up 24 weeks)											
1 Colombo 2010	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	very serious[g]	none	8/160 (5%)	2/79 (2.5%)	RR 1.98 (0.43 to 9.08)	25 more per 1000 (from 14 fewer to 205 more)	⊕OOO VERY LOW
Severe adverse events – CSA 5 mg/kg/day at weekends only (follow-up 24 weeks)											
1 Colombo 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[g]	none	1/160 (0.6%)	0/79 (0%)	RR 1.49 (0.06 to 36.18)	-	⊕OOO VERY LOW
Elevated serum creatinine – CSA 5 mg/kg/day at weekends only (follow-up 24 weeks)											
1 Colombo 2010	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[g]	none	8/160 (5%)	3/79 (3.8%)	RR 1.32 (0.36 to 4.83)	12 more per 1000 (from 24 fewer to 145 more)	⊕OOO VERY LOW

Elevated serum creatinine – CSA three-times weekly (at 2 consecutive visits) (follow-up 12 weeks)											
1 Thaci 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/42 (0%)	0/51 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE
Change in PASI – CSA three-times weekly (follow-up 12 weeks; better indicated by lower values)											
1 Thaci 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[h]	none	42	51	-	Mean PASI increase CSA: 2.7 to 9.9 Placebo: 3.0 to 11.9	⊕⊕OO LOW
Median time to relapse – CSA three-times weekly (follow-up 12 weeks; better indicated by higher values)											
1 Thaci 2002	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[i]	none	42	51	-	CSA: 98 days Placebo: 69 days	⊕⊕OO LOW
Time to relapse – CSA 5 mg/kg/day at weekends only (follow-up 24 weeks; better indicated by higher values)											
1 Colombo 2010	randomised trials	very serious[a]	no serious inconsistency	serious[j]	serious	none	160	79	p = 0.0233 (favours CSA)	-	⊕OOO VERY LOW

(a) Unclear method of randomisation and unclear allocation concealment and high dropout rate (30% - figures reported were per protocol)
(b) Confidence interval ranges from clinically important effect to no effect
(c) Surrogate measure for change in PASI
(d) Unclear allocation concealment
(e) Surrogate for time to relapse
(f) Unclear method of randomisation and unclear allocation concealment and high dropout rate (30%)
(g) Confidence interval crosses the boundary for clinical significance in favour of both treatment, as well as line of no effect
(h) No range or SD around change scores
(i) No range stated
(j) Only p-value provided

10.1.812 Evidence statements

In people with psoriasis, continuous ciclosporin administered for maintenance of remission was statistically significantly better than placebo for:

- Mean time to relapse and relapse rate after a maximum follow-up of 4 months (3 mg/kg/day CSA) [1 study; 41 participants; moderate to low quality evidence][343]
- Time-to-relapse (CSA three-times a week or 3 mg/kg/day) after a maximum follow-up of 12 or 24 weeks [2 studies; 224 participants; moderate quality evidence][341,342]

In people with psoriasis, there was no statistically significant difference between ciclosporin administered for maintenance of remission and placebo for:

- PASI75 at 24 weeks (CSA 5 mg/kg/day at weekends only) [1 study; 189 participants; very low quality evidence][340]
- Mean final PASI at 24 weeks (CSA 5 mg/kg/day at weekends only) [1 study; 189 participants; very low quality evidence][340]
- Maintaining at least mild psoriasis following PASI75 at 12 weeks (3-times weekly dosing) [1 study; 53 participants; low quality evidence][341]
- Mean time to relapse and relapse rate after a maximum follow-up of 4 months (1.5 mg/kg/day CSA) [1 study; 40 participants; low to very low quality evidence][343]
- Relapse rate after a maximum follow-up of 24 weeks (CSA 5 mg/kg/day at weekends only) [1 study; 189 participants; very low quality evidence][340]
- Withdrawal due to toxicity at 24 weeks (CSA 5 mg/kg/day at weekends only) [1 study; 239 participants; very low quality evidence][340]
- Severe adverse events at 24 weeks (CSA 5 mg/kg/day at weekends only) [1 study; 239 participants; very low quality evidence][340]
- Elevated creatinine at 24 weeks (CSA 5 mg/kg/day at weekends only) [1 study; 239 participants; very low quality evidence][340]

In people with psoriasis, there were no events with either ciclosporin administered for maintenance of remission or placebo for:

- Elevated creatinine (at two consecutive visits) at 12 weeks (3-times weekly dosing) [1 study; 93 participants; moderate quality evidence][341]

Evidence statements for individual studies where no original statistical analysis could be performed comparing ciclosporin and placebo administered for maintenance of remission:

- Time to relapse was longer with two- or three-times weekly ciclosporin than placebo after a maximum follow-up of 12 or 24 weeks [2 studies; 332 participants; low to very low quality evidence][340,341]
- There was a greater increase in PASI at 12 weeks during maintenance with placebo than three-times weekly ciclosporin [1 study; 93 participants; low quality evidence][341]

10.1.873 Subgroups and heterogeneity

For the outcomes of mean time to relapse and relapse rate from one study[343] there was a statistically significant difference between the dose subgroups. The time to relapse was significantly shorter and the relapse rate significant lower compared with placebo in the 3 mg/kg/day dose group compared with 1.5 mg/kg/day.

10.1.9 Intermittent (abrupt cessation) vs continuous ciclosporin for maintenance of remission

One study[344] defined intermittent dosing as ciclosporin being abruptly stopped after induction followed by an 12-week course of ciclosporin if relapse occurred, and continuous dosing as a tapering of the dose by 0.5mg/kg/day bi-monthly down to a maintenance level (the lowest marginally effective dose).

Two studies[345,346] defined intermittent ciclosporin as abruptly stopped ciclosporin being abruptly stopped after induction followed by an additional course of ciclosporin if relapse occurred, and continuous ciclosporin dosing as a tapering of the dose by 1 mg/kg/day until the treatment was stopped completely within 4 weeks, then an additional course was administered on relapse.

10.1.971 Evidence profile

Table 148: Intermittent (abrupt cessation) vs continuous ciclosporin for maintenance of remission

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous CSA	Intermittent (abrupt stop) CSA	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90) (follow-up 9 months)											
1 Chaidemenos, 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/24 (58.3%)	4/21 (19%)	RR 3.06 (1.19 to 7.87)	392 more per 1000 (from 36 more to 1309 more)	⊕⊕OO LOW
PASI75 (follow-up 9 months)											
1 Chaidemenos, 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	22/24 (91.7%)	13/21 (61.9%)	RR 1.48 (1.04 to 2.12)	297 more per 1000 (from 25 more to 693 more)	⊕OOO VERY LOW
PASI50 (follow-up 9 months)											
1 Chaidemenos	randomised trials	very serious[a]	no serious inconsistenc	no serious indirectne	no serious imprecision	none	23/24 (95.8%)	20/21 (95.2%)	RR 1.01	10 more per 1000	⊕⊕OO LOW

Quality assessment							Summary of findings				
, 2007			y	ss					(0.89 to 1.14)	(from 105 fewer to 133 more)	
Increased serum creatinine (follow-up 9 months)											
1 Chaidemenos , 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	2/24 (8.3%)	2/21 (9.5%)	RR 0.88 (0.13 to 5.68)	11 fewer per 1000 (from 83 fewer to 446 more)	⊕OOO VERY LOW
Hypertension (follow-up 9 months)											
1 Chaidemenos , 2007	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	1/24 (4.2%)	0/21 (0%)	RR 2.64 (0.11 to 61.54)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW
Time-to-relapse (follow-up 1 year)											
1 Ho, 1999	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	serious [b]	**Median time-to-relapse** Continuous: 113 days Intermittent: 109 days	173	192	HR 0.77 (0.61-0.98)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW
Median time to relapse (follow-up 2 years; Better indicated by higher values)											
1 Ho, 2001	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	30	46	-	Continuous : 119.5 days Intermittent: 115 days	⊕OOO VERY LOW

(a) Quasi-randomised and inadequate allocation concealment
(b) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit/harm to no clinically important benefit/harm
(c) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(d) Unclear allocation concealment and unblended
(e) No range stated

10.1.912 Evidence statements

In people with psoriasis, continuous ciclosporin was statistically significantly better than intermittent ciclosporin administered for maintenance of remission for:

- Clear/nearly clear (PASI90) at 9 months [1 study; 45 participants; low quality evidence][344]
- PASI75 at 9 months [1 study; 45 participants; very low quality evidence][344]
- Time-to-relapse after a maximum follow-up of 1 year [1 study; 365 participants; very low quality evidence] [345]

In people with psoriasis, there was no statistically significant difference between continuous and intermittent ciclosporin for maintenance of remission for:

- PASI50 at 9 months [1 study; 45 participants; low quality evidence][344]
- Increased creatinine at 9 months [1 study; 45 participants; very low quality evidence][344]
- Hypertension at 9 months [1 study; 45 participants; very low quality evidence][344]

Evidence statements for individual studies where no statistical analysis could be performed comparing intermittent (abrupt cessation) and continuous ciclosporin administered for maintenance of remission in people with psoriasis:

- Median time-to-relapse after a maximum follow-up of 2 years was longer with continuous than intermittent ciclosporin [1 study; 76 participants; very low quality evidence][346]

10.1.10 Intermittent (taper to withdraw) vs continuous (taper to minimum dose) ciclosporin for the maintenance of remission

Two studies induced remission using 3-5 mg/kg/day ciclosporin and defined the maintenance schedules as follows. 'Continuous' ciclosporin entailed dose reduction by 0.5-1.0 mg/kg/day each week and being continued at the lowest effective dose (in the range 0.5-3 mg/kg/day). If relapse occurred, the dose was increased to 3-5 mg/kg/day until remission was achieved, and the same procedure was repeated. 'Intermittent' ciclosporin entailed dose reduction by 0.5-1.0 mg/kg/day every other week followed by withdrawal. During withdrawal, topical steroids (10 g/day or less) of strong or medium potency were applied and if relapse occurred, the dose was increased to 3-5 mg/kg/day until remission was achieved. Treatment was withdrawn on remission and topical steroids were again applied.

10.1.10.1 Evidence profile

Table 149: Evidence profile for intermittent (taper to withdraw) vs continuous (taper to minimum dose) ciclosporin for maintenance of remission

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent (taper to cessation) CSA	Continuous CSA	Relative (95% CI)	Absolute	
Percentage change in PASI (follow-up 48 months; better indicated by higher values)											
1 Ozawa, 1999	randomised trials	very serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	20	17	-	MD 9.3 higher (6.05 to 12.55 higher)	⊕OOO VERY LOW
Final PASI (follow-up >48 months; better indicated by lower values)											
1 Ohtsuki, 2003	randomised trials	very serious[d]	no serious inconsistency	serious[e]	no serious imprecision	none	16	15	-	MD 3.56 higher (2.37 to 4.75 higher)	⊕OOO VERY LOW
Withdrawal due to toxicity (follow-up 48 months)											
1 Ozawa, 1999	randomised trials	very serious[a]	no serious inconsistency	serious[c]	very serious	none	2/33 (6.1%)	1/35 (2.9%)	RR 2.12 (0.20 to 22.31)	32 more per 1000 (from 23 fewer to 609 more)	⊕OOO VERY LOW
Hypertension (follow-up 1 year)											
1	randomis	serious	no serious	serious	very	none	10/61 (16.4%)	6/61	RR 1.67	66 more per 1000	⊕OOO

Quality assessment							Summary of findings				
Ohtsuki, 2003	ed trials	[d]	inconsistency	[e]	serious[b]			(9.8%)	(0.65 to 4.3)	(from 34 fewer to 325 more)	VERY LOW
Increased creatinine (follow-up 1 year)											
1 Ohtsuki, 2003	randomised trials	serious[d]	no serious inconsistency	serious[e]	very serious[b]	none	3/61 (4.9%)	2/61 (3.3%)	RR 1.5 (0.26 to 8.66)	16 more per 1000 (from 24 fewer to 251 more)	⊕OOO VERY LOW
Hyperuricaemia (follow-up 1 year)											
1 Ohtsuki, 2003	randomised trials	serious[d]	no serious inconsistency	serious[e]	very serious5	none	6/61 (9.8%)	3/61 (4.9%)	RR 2 (0.52 to 7.64)	49 more per 1000 (from 24 fewer to 327 more)	⊕OOO VERY LOW
Increased liver enzymes (follow-up 1 year)											
1 Ohtsuki, 2003	randomised trials	serious[d]	no serious inconsistency	serious[e]	very serious[b]	none	3/61 (4.9%)	0/61 (0%)	RR 7 (0.37 to 132.7)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW

(a) High dropout rate (continuous: 32%; intermittent: 29.5%) and patients lost due to relapse or remission not counted in analysis; unclear allocation concealment and blinding
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) No baseline data except PASI score so unclear if groups are balanced
(d) High dropout in both groups: 45/61 in intermittent group and 46/61 in continuous group (reasons in each group unclear); but data available for all for adverse event outcomes; unblended
(e) Many patients in intermittent group restarted ciclosporin earlier than in the protocol (so regimen more like the continuous treatment than planned).

10.1.1012 Evidence statements

In people with psoriasis, an intermittent (taper to withdrawal) schedule was statistically significantly better than a continuous schedule of ciclosporin administered for maintenance of remission for:

- Percentage change in PASI at 48 months [1 study; 37 participants; very low quality evidence][347]

In people with psoriasis, a continuous schedule was statistically significantly better than an intermittent (taper to withdrawal) schedule of ciclosporin administered for maintenance of remission for:

- Final PASI at 48 months [1 study; 31 participants; very low quality evidence][348]

In people with psoriasis, there was no statistically significant difference between intermittent (taper to withdrawal) vs continuous ciclosporin administered for maintenance of remission for:

- Withdrawal due to toxicity at 48 months [1 study; 68 participants; very low quality evidence][347]
- Hypertension at 1 year [1 study; 122 participants; very low quality evidence][348]
- Increased creatinine at 1 year [1 study; 122 participants; very low quality evidence][348]
- Hyperuricaemia at 1 year [1 study; 122 participants; very low quality evidence][348]
- Increased liver enzymes at 1 year [1 study; 122 participants; very low quality evidence][348]

10.1.1063 Subgroups and heterogeneity

For the outcomes of percentage change in PASI and final PASI the two studies[347,348] were not pooled as heterogeneity was present. This was not explained by any of the pre-defined subgroups; however, both studies were at high risk of bias owing to differences in baseline PASI score, which was higher in the intermittent group in both studies by 5.2-6.4 points, which was greater than the mean difference at the end point of the study in both cases. Additionally, both had a high drop-out rate in both the continuous and intermittent groups (32% and 29.5% for Ozawa[347] and 75.4% and 73.8% for Ohtsuki[348]).

10.1.11 Ciclosporin dosage comparisons for maintenance

One study induced remission using 2.5 vs 5.0 mg/kg/day ciclosporin and patients achieving remission entered a maintenance phase, receiving 2.5 or 5.0 mg/kg/day. The 5 mg/kg/day dose was tapered to 2.5 over 3 months and the dose was tapered in all participants from months 9-12.

10.1411.1 Evidence profile

Table 150: Evidence profile comparing ciclosporin dosage comparisons for maintenance

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ciclosporin low dose	Ciclosporin high dose	Relative (95% CI)	Absolute	
Severe adverse events (follow-up 18 months)											
1 Laburte, 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/119 (1.7%)	17/132 (12.9%)	RR 0.13 (0.03 to 0.55)	112 fewer per 1000 (from 58 fewer to 125 fewer)	⊕⊕OO LOW
Hypertension (follow-up 18 months)											
1 Laburte, 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	17/119 (14.3%)	20/132 (15.2%)	RR 0.94 (0.52 to 1.71)	9 fewer per 1000 (from 73 fewer to 108 more)	⊕OOO VERY LOW
Elevated creatinine (follow-up 18 months)											
1 Laburte, 1994	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/119 (21.8%)	73/132 (55.3%)	RR 0.4 (0.27 to 0.57)	332 fewer per 1000 (from 238 fewer to 404 fewer)	⊕⊕OO LOW
Elevated uric acid (follow-up 18 months)											
1 Laburte,	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	5/119 (4.2%)	8/132 (6.1%)	RR 0.69 (0.23 to 2.06)	19 fewer per 1000 (from 47 fewer to 64 more)	⊕OOO VERY LOW

Quality assessment							Summary of findings				
1994											
Change in PASI (follow-up 18 months; Better indicated by lower values)											
1 Laburte, 1994	randomised trials	very serious [a]	no serious inconsistency	no serious indirectness	serious [c]	none	119	132	-	2.5 mg: +1.7 5.0 mg: +2.7 See Table 151	⊕OOO VERY LOW

(a) Unclear method of randomisation, unclear allocation concealment, unblinded study
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) No SD provided

10.1.1112 Evidence statements

In people with psoriasis, 2.5 mg/kg/day ciclosporin was statistically significantly better than 5.0 mg/kg/day ciclosporin administered for maintenance of remission for:

- Severe adverse events at 18 months [1 study; 251 participants; low quality evidence][338]
- Elevated creatinine at 18 months [1 study; 251 participants; low quality evidence][338]

In people with psoriasis, there was no statistically significant difference between 2.5 and 5.0 mg/kg/day ciclosporin administered for maintenance of remission for:

- Hypertension at 18 months [1 study; 251 participants; very low quality evidence][338]
- Elevated uric acid at 18 months [1 study; 251 participants; very low quality evidence][338]

Table 151: Summary of non-analysed data for ciclosporin in the maintenance of remission

Study	Total N	Follow-up	Result				Treatment favoured
Change in PASI (during maintenance phase)							
Laburte 1994	251	18 months		**2.5 mg group**	**5 mg group**	**2.5 mg non-responders**	No clear difference (1 PASI point)
			Beginning of maintenance	4.2 (n=52)	3.6 (n=116)	3.9 (n=41)	
			End of maintenance	5.9 (n=40)	6.3 (n=79)	8.3 (n=25)	
			Change	+1.7	+2.7	+4.4	

Evidence statements for individual studies where no statistical analysis could be performed comparing different doses of ciclosporin administered for maintenance of remission:

- In people with psoriasis, there was no clinically relevant difference between 2.5 and 5.0 mg/kg/day ciclosporin for maintenance for change in PASI at 18 months [1 study; 251 participants; very low quality evidence][338].

10.1.12 Ciclosporin vs placebo for induction of remission in palmoplantar pustulosis

Note that the Reitamo study[349] included data from both a double-blind placebo-controlled phase and an open dose-finding phase in which non-responders from the placebo group were given 1.25mg/kg/day ciclosporin at week 4 and further dose increases at monthly intervals in steps of 1.25mg/kg/day up to maximum of 3.75mg/kg/day until week 16 if still unresponsive. Responders in the ciclosporin group continued previous treatment, while non-responders in ciclosporin group had the dose increased to 3.75mg/kg/day

10.16.12.1 Evidence profile

Table 152: Evidence profile comparing ciclosporin vs placebo for induction of remission in palmoplantar pustulosis

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CSA	Placebo	Relative (95% CI)	Absolute	
Improvement (follow-up 4 weeks)											
2 Erkko, 1998 Reitamo, 1993	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/46 (65.2%)	10/50 (20%)	RR 3.22 (1.78 to 5.85)	444 more per 1000 (from 156 more to 970 more) NNT = 2	⊕⊕⊕O MODERATE
Hypertension (follow-up 4 weeks)											
1 Erkko, 1998	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/27 (3.7%)	0/31 (0%)	RR 3.43 (0.15 to 80.83)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW
Serum creatinine increased (follow-up 4 weeks)											
1 Reitamo, 1993	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/19 (0%)	0/19 (0%)	-	-	⊕⊕⊕O MODERATE

Quality assessment							Summary of findings				
Hypertension (follow-up 2-12 months)											
1 Erkko, 1998	observational studies3	serious[d]	no serious inconsistency	serious[e]	serious[f]	none	7/27 (25.9%)	0/31 (0%)	RR 17.14 (1.02 to 286.86)	0 more per 1000 (from 0 more to 0 more)	⊕OOO VERY LOW
Serum creatinine increased (follow-up 2-12 months)											
1 Erkko, 1998	observational studies[c]	serious[d]	no serious inconsistency	serious[e]	very serious[b]	none	2/27 (7.4%)	0/31 (0%)	RR 5.71 (0.29 to 114.05)	0 more per 1000 (from 0 fewer to 0 more)	⊕OOO VERY LOW
Improvement (open phase) (follow-up 4 months)											
1 Reitamo, 1993	observational studies[c]	serious[d]	no serious inconsistency	serious[e]	serious[b]	none	10/14 (71.4%)	10/14 (71.4%)	RR 1 (0.63 to 1.6)	0 fewer per 1000 (from 264 fewer to 429 more)	⊕OOO VERY LOW
Relapse rate (open phase) (follow-up 4 months)											
1 Reitamo, 1993	observational studies[c]	serious[d]	no serious inconsistency	serious[g]	very serious[b]	none	0/19 (0%)	2/13 (15.4%)	RR 0.14 (0.01 to 2.7)	132 fewer per 1000 (from 152 fewer to 262 more)	⊕OOO VERY LOW
Relapse rate (withdrawal phase) (follow-up 6 months)											
1 Reitamo, 1993	observational studies[c]	serious[d]	no serious inconsistency	serious[g]	very serious[b]	none	6/10 (60%)	8/12 (66.7%)	RR 0.9 (0.47 to 1.72)	67 fewer per 1000 (from 353 fewer to 480 more)	⊕OOO VERY LOW

(a) Unclear allocation concealment and blinding
(b) Confidence interval crosses the boundary for clinical significance in favour of both interventions, as well as line of no effect
(c) Open phase of RCT
(d) Unclear if still matched for demographic characteristics

(e) Open phase of trial (patients originally randomised to placebo received ciclosporin if no response)
(f) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important harm to no clinically important harm)
(g) Surrogate outcome for time-to-relapse and follow-up after open phase of trial (patients originally randomised to placebo received ciclosporin if no response)

10.1.1212 Evidence statements

In people with palmoplantar pustulosis, ciclosporin was statistically significantly better than placebo for:

- Improvement at 4 weeks [2 studies; 96 participants; moderate quality evidence][349,350]

In people with palmoplantar pustulosis, placebo was statistically significantly better than ciclosporin for:

- Hypertension at 12 months [1 study; 58 participants; very low quality evidence][350]

In people with palmoplantar pustulosis, there was no statistically significant difference between ciclosporin and placebo for:

- Hypertension at 4 weeks [1 study; 58 participants; very low quality evidence][350]
- Increased serum creatinine at 12 months [1 study; 58 participants; very low quality evidence][350]
- Improvement at 4 months during open phase [1 study; 28 participants; very low quality evidence][349]
- Relapse rate during open (4 months) and withdrawal (6 months) phases [1 study; 32 and 22 participants, respectively; very low quality evidence][349]

In people with palmoplantar pustulosis, there were no events with either ciclosporin or placebo for:

- Increased serum creatinine at 4 weeks [1 study; 38 participants; moderate quality evidence][349]

10.2 Time to maximum effect

10.2.1 Evidence profiles

10.2.1.1 Ciclosporin

Quality assessment							Summary of findings		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients: Ciclosporin	Effect	Quality
Median time to 70% or 90% reduction in BSA (follow-up 16 weeks; better indicated by lower values)									
1 Shupack 1997	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	serious[c]	none	181	Median time to 70% reduction in BSA: 8 weeks Median time to 90% reduction in BSA: 12 weeks	⊕OOO VERY LOW
Median time to 75% reduction in BSA (follow-up 12 weeks; better indicated by lower values)									
1 Ho 1999	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	serious[c]	none	365	Median time to satisfactory clinical response (≥75% reduction in BSA): 9.7 weeks	⊕OOO VERY LOW
Mean time to PASI80 (follow-up to remission; better indicated by lower values)									
1 Ozawa 1999	observational studies[a]	no serious limitations [d]	no serious inconsistency	serious[e]	serious[f]	none	37	Mean time to remission (decrease in PASI of 80%): 15.4 weeks (4.7 months in continuous group and 3.0 months in intermittent group – but both received the same dose schedule during the induction period)	⊕OOO VERY LOW
Mean time to maximum response (mean PASI); (follow-up 12 weeks; better indicated by lower values)									
1 Flytstrom 2008	observational studies[a]	no serious limitations[g]	no serious inconsistency	no serious indirectness	very serious[h]	none	31	Mean PASI score still decreasing at 12 weeks CSA response greatest over the first 4 weeks By 12 weeks the mean % improvement in PASI was 72%	⊕OOO VERY LOW

Mean time to maximum response (mean PASI); (follow-up 24 weeks; better indicated by lower values)									
1 Gumusel 2011	observational studies[a]	no serious limitations[g]	no serious inconsistency	no serious indirectness	very serious[h]	none	17	Maximal response based on PASI score appeared to be at 16 weeks	⊕OOO VERY LOW
Mean time to maximum response (mean PASI); (follow-up 16 weeks; better indicated by lower values)									
1 Heydendael 2003	observational studies[a]	no serious limitations[g]	no serious inconsistency	no serious indirectness	very serious[h]	none	42	Maximal response based on PASI score appeared to be at 12 weeks By 16 weeks the mean % improvement in PASI was 72%	⊕OOO VERY LOW
Mean time to maximum response (mean % improvement in PASI); CSA (follow-up 24 weeks; better indicated by lower values)									
1 Christophers 1992	randomised trials	very serious[i]	no serious inconsistency	serious[j]	very serious[h]	none	Remaining on 1.25 mg/kg/d: 26 Remaining on 2.5 mg/kg/d: 68	Mean % change in PASI beginning to plateau at 8-12 weeks in both dose groups (approaching PASI75 at higher dose by this time point)	⊕OOO VERY LOW

1 *(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference to the*
2 *comparator arm*
3 *(b) Non-randomised, non-comparative induction period of maintenance trial*
4 *(c) No range given for median time*
5 *(d) Non-comparative induction period of maintenance trial*
6 *(e) Mean is inappropriate for time-to-event data*
7 *(f) No SD given for mean*
8 *(g) Non-comparative data from RCT*
9 *(h) Results interpreted from graphical representation of data*
10 *(i) Unclear allocation concealment, unblinded and unclear dropout rate*
11 *(j) Data based only on those who did not require dose escalation (24% of 1.25 mg/kg group and 62% of 2.5 mg/kg group)*
12

10.2.1.32 Methotrexate

Quality assessment							Summary of findings		
							No of patients	Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Methotrexate		

						considerations			
Mean time to maximum response (% change in PASI); MTX (follow-up 16 weeks; better indicated by lower values)									
1 Saurat 2008	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	110	Maximal response not achieved during 16 week trial	⊕OOO VERY LOW
Mean time to maximum response (mean PASI); MTX (follow-up 24 weeks; better indicated by lower values)									
1 Ho 2010	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	20	Response beginning to plateau at 4-6 months based on mean PASI score over time, , but there is still a very gradual continued improvement over this period	⊕OOO VERY LOW
Mean time to maximum response (mean PASI); MTX (follow-up 12 weeks; better indicated by lower values)									
1 Flytstrom 2008	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	37	Mean PASI score still decreasing at 12 weeks By 12 weeks the mean % improvement in PASI was 58%	⊕OOO VERY LOW
Mean time to maximum response (mean PASI); MTX (follow-up 16 weeks; better indicated by lower values)									
1 Heydendael 2003	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	43	Maximal response based on PASI score appeared to be at 12 weeks By 16 weeks the mean % improvement in PASI was 64% Note: HR for time-to PASI75 0.61 (0.36 to 1.04) in favour of CSA; HR for time-to PASI90 = 1.15 in favour of MTX	⊕OOO VERY LOW
Mean time to maximum response (mean PASI); MTX (follow-up 24 weeks; better indicated by lower values)									
1 Gumusel 2011	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	17	Maximal response based on PASI score appeared to be at 8 weeks	⊕OOO VERY LOW

1 *(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference*
2 *(b) Non-comparative data from RCT*
3 *(c) Results interpreted from graphical representation of data*
4

10.2.153 Acitretin

Quality assessment	Summary of findings

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients: Acitretin	Effect	Quality
Mean time to maximum response (% improvement in BSA); acitretin (follow-up 24 weeks; better indicated by lower values)									
1 Goldfarb 1988	observational studies[a]	no serious limitations[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	17	Improvement in global score and %BSA based on pooled data for all doses of acitretin was maximal at 20 weeks based on graphical presentation of change over time (0-24 weeks)	⊕OOO VERY LOW
Mean time to maximum response (mean % improvement in PASI); acitretin (follow-up 24 weeks; better indicated by lower values)									
1 Lassus 1987	randomised trials	serious[d]	no serious inconsistency	serious[e]	very serious[c]	none	60 (20 in each group)	Mean % improvement in PASI score was still increasing at 2 months on 10, 25 and 50 mg/day acitretin	⊕OOO VERY LOW
Mean time to maximum response (mean % improvement in PASI); acitretin (follow-up 24 weeks; better indicated by lower values)									
1 Berbis 1989	randomised trials	serious[f]	no serious inconsistency	serious[g]	very serious[c]	none	Increasing dose: 21 Constant dose: 19 Decreasing dose: 19	All dosing schedules: mean % change in PASI still increasing at 6 weeks Increasing dosing schedule: greater rate of % improvement in PASI still apparent at 6 weeks than the decreasing or constant dosing schedules (which were increasing more gradually)	⊕OOO VERY LOW

(a) Although the data are taken from randomised trials the benefit of control data is not being utilised as considerations are being made based on single interventions without reference
(b) Non-comparative data from RCT
(c) Results interpreted from graphical representation of data
(d) Unclear allocation concealment and blinding not explained fully
(e) Disease severity at baseline not reported and steroids administered on request (numbers using differed between the groups)
(f) Unclear allocation concealment
(g) Higher proportion of men in increasing dose group and more with pustular and guttate psoriasis in decreasing dose group

10.282 Data summary table

Table 153: Absolute data on time to maximum effect or time to remission

Study	Total N	Follow-up	Intervention	Result	Notes
Time to remission					

Study	Total N	Follow-up	Intervention	Result	Notes
Shupack	181	16 weeks	CSA	Median time to 70% reduction in BSA: 8 weeks Median time to 90% reduction in BSA: 12 weeks	Non-randomised induction period of maintenance trial (CSA: 5 mg/kg)
Ho 1999	365	12 weeks	CSA	Median time to satisfactory clinical response (≥75% reduction in BSA): 9.7 weeks	Non-randomised induction period of maintenance trial (CSA: 2.5-5 mg/kg)
Ozawa 1999	37	To remission (maximum not stated)	CSA	Mean time to remission among responders (decrease in PASI of 80%): 15.4 weeks (4.7 months in continuous group and 3.0 months in intermittent group – but both received the same dose schedule during the induction period)	Induction period of maintenance trial (CSA: 3-5 mg/kg)
Time to maximum response (based on graphical representation)					
Saurat 2008	158	16 weeks	MTX vs placebo	MTX maximal response not achieved during 16 week trial (curve for mean % improvement in PASI had reached 54.3% but still increasing gradually)	MTX: 7.5 mg increased to a maximum of 25 mg/wk as needed and tolerated Folic acid supplement
Ho 2010	36	24 weeks	MTX vs placebo	MTX response beginning to plateau at 4-6 months based on mean PASI score over time, but there is still a very gradual continued improvement over this period The mean % improvement in PASI had reached 73.9% by 6 months	MTX: 2.5-5.0 mg/wk to assess safety then 10 mg/wk up to 30 mg/wk Folic acid supplement
Flytstrom 2008	68	12 weeks	MTX vs CSA	Mean PASI scores for both MTX and CSA still decreasing gradually at 12 weeks CSA response appears to be more rapid, with greater improvement over the first 4 weeks By 12 weeks the mean % improvement in PASI was 58% in MTX group and 72% in CSA group	MTX: 7.5 mg/wk (3-divided dose) up to 15 mg/wk (plus folic acid) CSA: 3 mg/kg/d (divided into 2 doses) up to 5 mg/kg/d
Heydendael 2003	62	16 weeks	MTX vs CSA	Maximal response based on PASI score appeared to be at 12 weeks for both MTX and CSA, with the PASI score *increasing* slightly between 12 and 16 weeks By 16 weeks the mean % improvement in PASI was 64% in MTX group and 72% in CSA group	MTX: 15 mg/wk (3-divide dose) up to 22.5 mg/wk CSA: 3 mg/kg/d (divided into 2 doses) up to 5 mg/kg/d
Goldfarb 1988	37	24 weeks	Acitretin dosing	Improvement in global score and % BSA based on pooled data for all doses of acitretin were maximal at 20 weeks based on graphical presentation of change over time (0-24 weeks) The % BSA decreased from 35% to 13% by 24 weeks	10, 25, 50 or 75 mg/day acitretin (plus open phase)
Lassus 1987	80	8 weeks	Acitretin	Mean % change in PASI score was still increasing at 2 months (based on	10, 25 or 50 mg/day acitretin (plus open

Study	Total N	Follow-up	Intervention	Result	Notes
			dosing	graphical representation of % change in PASI) on 10, 25 and 50 mg/day acitretin	phase) Patients using potent steroid concomitantly
Berbis 1989	58	6 weeks	Acitretin dosing schedule	The increasing dosing schedule of acitretin appeared to still be effecting a greater rate of % improvement in PASI at 6 weeks than the decreasing or constant dosing schedules, which were also still improving, although more gradually By 6 weeks the mean % improvement in PASI was approximately 55-65% across the three regimens	Acitretin: 10 up to 50 mg/day vs 50 down to 10 mg/day vs 30 mg/day
Christophers 1992	217	12 weeks	CSA	Mean % change in PASI was beginning to plateau at 8-12 weeks (and the response was approaching PASI75 at higher dose by this time point)	Doses initially 1.25 or 2.5 mg/kg (data based on those who did not require dose escalation: 24% of 1.25 mg/kg group and 62% of 2.5 mg/kg group)
Gumusel 2011	34	24 weeks	MTX vs CSA	Mean PASI scores reached maximum response for MTX at 8 weeks and CSA at 16 weeks	MTX: 15 mg/wk (single dose) for first 3 months then 10 mg/wk (single dose) for second 3 months (plus folic acid) CSA: 5 mg/kg/d (divided into 2 doses) for first 3 months then 2.5-3.2 mg/kg/d for second 3 months

1

10.2.3 Evidence statements

Evidence statements for individual studies that provide data regarding the time to remission or time to maximum response for systemic non-biological therapies (no statistical analysis could be performed).

10.2.3.1 Ciclosporin

In people with psoriasis, the time to remission when taking ciclosporin varied between studies:

- Median time to 70-90% reduction in BSA ranged from 8-12 weeks [2 studies; 546 participants; very low quality evidence][342,345]
- Mean time to PASI80: 15.4 weeks [1 study; 37 participants; very low quality evidence][347]

In people with psoriasis, the time to maximum response when taking ciclosporin varied between studies:

- Mean PASI score still decreasing gradually at 12 weeks (although most rapid improvement was seen over the first 0-8 weeks) [1 study; 31 participants; very low quality evidence][325]
- Mean PASI score reached maximal response at 12 weeks [1 study; 42 participants; very low quality evidence][326]
- Mean PASI score reached maximal response at 16 weeks [1 study; 17 participants; very low quality evidence][327]
- Mean percentage change in PASI reaching a maximum between 8 and 12 weeks [1 study; 94 participants; very low quality evidence][339]

Summary

- The majority of the evidence suggests that 2.5-5.0mg/kg/day ciclosporin leads to remission or maximum response after between 9 and 12 weeks of treatment

10.2.3.2 Methotrexate

In people with psoriasis, the time to maximum response when taking methotrexate varied between studies:

- Mean percentage improvement in PASI score still increasing gradually at 16 weeks [1 study; 110 participants; very low quality evidence][323]
- Mean PASI score reached a maximum response between 4 and 6 months [1 study; 20 participants; very low quality evidence][324]
- Mean PASI score still decreasing gradually at 12 weeks [1 study; 37 participants; very low quality evidence][325]
- Mean PASI score reached maximal response at 12 weeks [1 study; 43 participants; very low quality evidence][326]
- Mean PASI score reached maximal response at 8 weeks [1 study; 17 participants; very low quality evidence][327]

Summary

- The majority of the evidence suggests that methotrexate leads to remission or maximum response after between 16 and 24 weeks of treatment, although the higher initial dose of 15 mg/wk in two studies[326,327] appeared to achieve maximal response after 8-12 weeks of treatment

10.2.313 Acitretin

In people with psoriasis, the time to maximum response when taking acitretin varied between studies:

- Mean improvement in global score and percentage coverage of body surface area (pooled data for all doses of acitretin) were maximal at 20 weeks [1 study; 37 participants; very low quality evidence][330]
- Mean percentage improvement in PASI score was still increasing at 2 months on 10, 25 and 50 mg/day acitretin [1 study; 60 participants; very low quality evidence][329]
- Percentage improvement in PASI had not reached a maximum by 6 weeks for all dosing schedules; however, the increasing dosing schedule showed a greater continued rate of improvement at 6 weeks than the decreasing or constant dosing schedules, which were increasing gradually [1 study; 58 participants; very low quality evidence][332]

Summary

- The evidence suggests that acitretin may lead to remission or maximum response after approximately 20 weeks of treatment, and that an increasing dose may allow greater improvement than a deceasing or constant dosing schedule[332]

10.2.14 Economic evidence

An economic evaluation should ideally compare all relevant alternatives. No applicable studies of good enough methodological quality were identified comparing all interventions of interest – acitretin, ciclosporin and methotrexate – in the treatment of patients with psoriasis.

Three studies[276,351,352] were included that included the relevant comparison between ciclosporin and methotrexate and best supportive care. These are summarised in the economic evidence profiles below (Table 154, Table 155, Table 156 and Table 157). See also the full study evidence tables in Appendix I.

Five studies[273,274,353-355] were selectively excluded due to their poor applicability and very serious methodological limitations. These are detailed in Appendix G.

No relevant economic evaluations comparing acitretin with either ciclosporin or methotrexate were identified.

Table 154: Methotrexate versus ciclosporin versus best supportive care – economic study characteristics

Study	Limitations	Applicability	Other comments
Opmeer 2004[351]	Potentially serious limitations(a)	Partially applicable(b)	• Cost-minimisation analysis of an RCT (Heydendael 2003[326]) • Patients with moderate to severe psoriasis • Time horizon: 12 wks treatment; 36 wks follow-up • Comparators: methotrexate and ciclosporin • Costs: Direct medical costs (medication, diagnostic procedures, laboratory tests, visits to healthcare providers, therapies used during follow-up)

Study	Limitations	Applicability	Other comments
Sizto 2008[352]	Potentially serious limitations(c)	Directly applicable(d)	• Decision analytic model • Patients with moderate to severe psoriasis • Treatment effects: probabilities of PASI 50, 75 and 90 estimated through systematic review and network meta-analysis of RCTs[356] • Time horizon: not stated • Comparators: methotrexate and ciclosporin and best supportive care(e) • Costs: Drugs and monitoring (excludes cost of dermatology and GP visits)
Woolacott 2006[276]	Potentially serious limitations(f)	Directly applicable(g)	• Decision analytic model • Patients with moderate to severe psoriasis • Treatment effects: probabilities of PASI 50, 75 and 90 estimated through systematic review and network meta-analysis of RCTs (by the same authors) • Time horizon: up to 10 years • Comparators: methotrexate and ciclosporin and best supportive care(h) • Costs: Drugs, monitoring, outpatient visits, inpatient visits

(a) Short time horizon (1 year); assumption informing treatment effects based on single RCT, not entire evidence base; relatively old cost estimates (1999/2000); no sensitivity analysis reported
(b) Costing perspective is Dutch society: some uncertainty about applicability of Dutch estimates of resource use and unit costs; cost-minimisation method
(c) Time horizon not stated; systematic review and network meta-analysis does not include all recent and relevant studies of ciclosporin and methotrexate; estimates of long-term effectiveness/withdrawal of treatments not stated; excludes important costs of outpatient dermatology and GP visits; funded by Abbott laboratories (makers of Adalimumab – biological therapy included in the analysis)
(d) No discounting rates reported for costs or effects
(e) Best supportive care not defined explicitly, but cost £117 per year.
(f) Analysis was mainly focused on evaluation of etanercept and efalizumab – ciclosporin and methotrexate were evaluated as part of one probabilistic scenario analysis; systematic review and network meta-analysis does not include all recent and relevant studies of ciclosporin and methotrexate; cost of ciclosporin has decreased by one-third since analysis was undertaken
(g) Discounting rates were 6% for costs and 1.5% for benefits instead of 3.5% for both
(h) Best supportive care defined as two outpatient visits per year, an annual cost of £113.

Table 155: Methotrexate versus best supportive care – economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Sizto 2008	£3,844 (a)	-129 QALYs (b)	Dominates	Costs 95% CI: -5049 to -2722 QALYs 95% CI: 0.078 to 0.185 Visual inspection of 95% confidence interval ellipses indicates that methotrexate dominates best supportive care in 100% of simulations
Woolacott 2006	-£4,223(c)	0.126 QALYs	Dominates	Cost 95% CI: -4604 to -3224

Study	Incremental cost	Incremental effects	ICER	Uncertainty
				QALYs 95% CI: 0.072 to 0.182 At thresholds of £20K and £30K per QALY, methotrexate has a 100% probability of being more cost-effective than best supportive care.

(a) 2005/06 UK Pounds; does not include costs of outpatient of GP visits
(b) Time horizon not reported
(c) 2004/05 UK Pounds

Table 156: Ciclosporin versus best supportive care – economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Sizto 2008	-£1987 (a)	0.079 QALYs (b)	Dominates	Costs 95% CI: -3313 to -597 QALYs 95% CI: 0.044 to 0.116 Visual inspection of 95% confidence interval ellipses indicates that ciclosporin dominates best supportive care in 100% of simulations
Woolacott 2006	-£452 (c)	0.122 QALYs	Dominates	Cost 95% CI: -795 to 41 QALYs 95% CI: 0.072 to 0.175 Probability of being more cost-effective than best supportive care could not be determined from the study report.

(a) 2005/06 UK Pounds; does not include costs of outpatient of GP visits
(b) Time horizon not reported
(c) 2004/05 UK Pounds

Table 157: Ciclosporin versus methotrexate – economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Opmeer 2004	£1,013 (d)	Assumed same (e)		Visual inspection of box and whisker plot indicate that costs accrued during treatment were significantly different between strategies, but this did not hold during 36 weeks follow-up
Sizto 2008	£1,857 (f)	-0.05 QALYs (g)	Dominated	Costs 95% CI: 1736 to 2125 QALYs 95% CI: -0.034 to -0.069 95% CI ellipses overlap, but visual inspection indicates that methotrexate dominates ciclosporin in approximately 80% of simulations
Woolacott 2006	£3,771 (h)	-0.004 QALYs	Dominated	Cost 95% CI: 3265 to 3809 QALYs 95% CI: 0 to -0.007 At a threshold of £20K per QALY, methotrexate has a 100% probability of being more cost-effective than ciclosporin; at £30K per QALY, this probability is 99%

(d) Converted from 1999 Dutch Euros
(e) Cost minimisation approach assumes the clinical outcomes are the same for both strategies
(f) 2005/06 UK Pounds; does not include costs of outpatient of GP visits
(g) Time horizon not reported

(h) 2004/05 UK Pounds

Despite its limitations and partial applicability, the analysis by Opmeer has been included in this review because it is the only study to be based on prospectively collected resource use data associated with treatment with ciclosporin and methotrexate during both a trial period and follow-up. The analysis shows that the biggest difference in cost between the treatments is driven by the difference in drug cost during the first 16 weeks during which ciclosporin is more costly. During follow-up however, the difference between the two treatments becomes less significant due to the similar use of other therapies, such as UVB phototherapy, day care treatments and topicals after treatment with the systemic therapies has stopped. In clinical practice, it is unlikely that duration of treatment with these drugs will be identical. Ciclosporin is often given for a shorter duration than methotrexate due to the increased risk of nephrotoxicity with longer term use. Methotrexate is often given for a longer period as its maximum effectiveness may not even be observed by 16 weeks. Therefore, it is unlikely that the cost differences between ciclosporin and methotrexate would diminish as rapidly in clinical practice as the results of Opmeer and colleagues would suggest.

The studies by Sizto and Woolacott clearly show that treatment with methotrexate or ciclosporin to be cost saving compared to best supportive care or no treatment. They also demonstrate methotrexate to be cost saving compared to ciclosporin; that is, producing greater quality of life gains for less NHS resource. However, the limitations of these studies are potentially serious insofar as their conclusions about cost-effectiveness are based on a now incomplete evidence base and out-of-date unit costs. The Sizto analysis does not include all the relevant RCT data for ciclosporin (missing studies include by Van Joost and colleagues[336], Ellis and colleagues[333] and Guenther and colleagues[335]) which is likely why it has performed more poorly compared to methotrexate than in the analysis by Woolacott and colleagues. The study by Woolacott includes clinical evidence published only up until April 2004, which means that it does not include the more recent RCTs by Ho and colleagues[324], Saurat and colleagues[323] and Flytstrom and colleagues[325], the last in which ciclosporin is shown to be more effective than methotrexate. Additionally, the cost of ciclosporin has decreased by about one-third since these evaluations were undertaken.

10.2.4.1 New cost-effectiveness analysis

New analysis was not prioritised for this question. Despite the existing economic evidence having some potentially serious limitations, the GDG believe that the conclusions of these analyses (i.e. that methotrexate is more cost-effective than ciclosporin) are still very likely to be true and that a new cost-effectiveness analysis is unlikely to inform recommendations further. On that basis, this question was not considered a high priority for de novo modelling and would only have been undertaken if other higher priority areas, such as topical therapies and second-line biological therapies, were deprioritised. Therefore, the GDG made their recommendations about which systemic treatments should be offered and when based on published clinical and cost-effectiveness evidence.

10.2.4.2 Evidence statements

- No cost-effectiveness analyses were identified comparing all three interventions of interest – acitretin, ciclosporin and methotrexate – in the treatment of patients with psoriasis.
- Two cost-effectiveness analyses showed methotrexate and ciclosporin to be cost saving compared to best supportive care in the treatment of patients with moderate to severe plaque psoriasis. These studies are directly applicable and have potentially serious limitations.
- Two cost-effectiveness analyses and one cost-minimisation analysis show methotrexate to be cost saving compared to ciclosporin in the treatment of patients with moderate to severe plaque psoriasis. Overall, the studies contributing to this evidence are partially or directly applicable and have potentially serious limitations.

- No economic evidence is available to estimate the relative cost-effectiveness of acitretin.

10.3 Recommendations and link to evidence

Recommendations	**72.Only use systemic therapy in specialist settings.**
Recommendations on discussion and monitoring	**73.When offering systemic therapy, tailor the choice of agent and dosing schedule to the needs of the individual and include consideration of:** • **the person's age** • **disease phenotype, pattern of activity and previous treatment history** • **disease severity and impact** • **the presence of psoriatic arthritis (in consultation with a rheumatologist)** • **conception plans** • **comorbidities** • **the person's views.** **74.Be aware of the benefits of, contraindications to and adverse effects associated with systemic treatments. Explain the risks and benefits to people undergoing this treatment using absolute risks and natural frequencies when possible. Support and advice should be provided by healthcare professionals who are trained and competent in the use of systemic therapies.** **75.Monitor people using systemic treatment for all types of psoriasis in accordance with national and local drug guidelines and policy. Take appropriate action in the event of laboratory abnormalities or adverse events.** **76.Offer adjunctive topical therapy to optimise treatment outcomes.** **77.Offer people with psoriasis who are starting treatment with a systemic non-biological or biological drug the opportunity to participate in long-term safety registries (for example the British Association of Dermatologists Biologic Interventions Register).**
Recommendations on choice of drugs (systemic non-biological therapy)	**78.Offer systemic therapy to people with psoriasis if:** • **it cannot be controlled with topical therapy and** • **it has a significant impact on physical, psychological or social wellbeing and** • **one or more of the following apply:** – **psoriasis is extensive (for example, BSA of more than 10% affected or a PASI score of more than 10) or** – **psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for**

example severe nail disease or involvement at high-impact sites) or

- **phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).**

79. In people with both active psoriatic arthritis and psoriasis that fulfils the criteria for systemic therapy (see recommendation 78) consider the choice of systemic agent in consultation with a rheumatologist. For further information see 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal guidance 199).

80. Offer methotrexate[z] as the first choice of systemic agent for people with psoriasis that fulfils the criteria for systemic therapy (see recommendation 78) except in the circumstances described in recommendations 81 and 82.

81. When considering the risks and benefits of treating any type of psoriasis with methotrexate, be aware that methotrexate can cause a clinically significant rise in transaminases and that long-term therapy may be associated with liver fibrosis (see recommendations 91 to 95).

82. Offer ciclosporin[aa] as the first choice of systemic agent for people with psoriasis that fulfils the criteria for systemic therapy (see recommendation 78) and who:

- **need rapid or short-term disease control (for example a psoriasis flare) or**
- **have palmoplantar pustulosis or**
- **are considering conception (both men and women) and systemic therapy cannot be avoided.**

83. Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate.

84. Consider acitretin for adults, and in exceptional cases only for children[bb], in the following circumstances:

- **if methotrexate and ciclosporin are not appropriate or have failed or**
- **for people with pustular forms of psoriasis.**

z At the time of publication (May 2012), methotrexate did not have an official dose recommendation for this indication in children and the SPC states that there is no experience in young children

[aa] At the time of publication (May 2012), ciclosporin did not have an official dose recommendation for this indication in children, but there was no specific contraindication for use in the age group..

[bb] At the time of publication (May 2012), acitretin only had UK marketing authorisation for this indication in children if the benefits outweigh the risks as it is contraindicated. Informed consent should be obtained and documented.

Recommendations on drug regimens for systemic therapy	**85. Use incremental dosing of methotrexate (for example, starting with an initial dose of 5–10 mg once a week) in adults and gradually increase the dose up to the target dose of 25 mg a week. Assess the treatment response after 3 months at the target dose of methotrexate and stop treatment if the response is inadequate (for example, a decrease of less than 75% in PASI score or a decrease of less than 50% in PASI score and 5 points in DLQI score).** **86. Use the lowest possible therapeutic dose of methotrexate to maintain remission.** **87. Use 2.5–3 mg/kg a day of ciclosporin[cc] for adults and children. Escalate to 5 mg/kg a day after 4 weeks only when there is no response to the lower dose or when rapid disease control is necessary (for example in severe unstable disease). Assess the treatment response after 3 months at the optimum dose of ciclosporin and stop treatment if the response is inadequate (for example, less than a 75% decrease in PASI score or less than a 50% decrease in PASI score and less than 5 points in DLQI score).** **88. Use the lowest possible therapeutic dose of ciclosporin to maintain remission for up to 1 year. Consider other treatment options when disease relapses rapidly on stopping ciclosporin therapy (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months of stopping treatment). Do not use ciclosporin continuously for more than 1 year unless disease is severe or unstable and other treatment options cannot be used.** **89. Use incremental dosing of acitretin to minimise mucocutaneous side effects and achieve a target dose of 25 mg daily in adults. Consider dose escalation to a maximum of 50 mg daily when no other treatment options are available.**
Recommendations on reviewing treatment response	**90. When reviewing response to systemic therapy, take into account:** • **disease severity compared with baseline (for example, PASI baseline to endpoint score)** • **control of psoriatic arthritis disease activity (in consultation with a rheumatologist if necessary)** • **the impact of the disease on the person's physical, psychological and social wellbeing** • **the benefits versus the risks of continued treatment** • **the views of the person and, in children, their family.**
Recommendations on methotrexate and monitoring for hepatotoxicity	**See section 11.4**

[cc] At the time of publication (October 2012), ciclosporin did not have an official dose recommendation for this indication in children, but there was no specific contraindication for use in the age group..

Future research recommendations	**18. In people with psoriasis, are there any clinical (for example, demographic, phenotypic) or laboratory (for example genetic or immune markers) that identify people who will respond to treatment with, or who will remain in remission following, treatment with methotrexate or ciclosporin?** **19. What is the most effective, safe and cost effective methotrexate dosing regimen to treat psoriasis and what is the role of folic acid in reducing efficacy or improving safety of methotrexate?** **20. In children with psoriasis, what the effective, safe and cost effective use of methotrexate, ciclosporin and acitretin?** **21. In people with palmoplantar pustulosis, what are the clinical effectiveness, safety, tolerability and cost effectiveness of acitretin and methotrexate?**
Relative values of different outcomes	The GDG agreed to prioritise the following outcomes when considering the evidence: • PASI75 (or clear/nearly clear) • Time to relapse • Time to remission • Serious adverse events • Withdrawal due to toxicity Of the outcomes listed as priorities, the GDG were particularly interested in data from long-term studies. When considering the evidence, the GDG chose outcome measures that reflect impact on quality of life (as indicated by a change in the Dermatology Life Quality Index (DLQI), and objective assessments of skin involvement, namely the 'physician's global evaluation' of clear/nearly clear, and various measures derived from the PASI including final PASI and improvement in the Psoriasis Area and Severity Index (PASI) as reported by PASI 75 and PASI 50 (i.e. 75% and 50% improvement from baseline respectively). Achievement of a PASI 75 and clear/nearly clear is an accepted 'gold standard' indicator of clinical effectiveness and tends to be reported in trials. PASI 50 is related to PASI 75, but has been specifically included as an indication of the minimum level of efficacy required to continue with therapy. These efficacy outcomes are also consistent with the NICE defined treatment response criteria for biological therapy where therapy can be continued only in those who achieve either a PASI 75, or PASI 50 and a fall in the DLQI of 5 points. The GDG looked for evidence of efficacy in both the short term (12-16 weeks, induction of remission) as well as in the longer term, and relapse rates following cessation of treatment. Clearly the toxicity and tolerability of systemic treatments are major considerations in relation to drug choice, and the adverse effects of each of the interventions are detailed in the relevant drug -specific Summary of Product Characteristics (SPC). However, the comparative

	toxicities of the different drugs are important given there may need to be a trade off between effectiveness and side effects. The GDG therefore looked for evidence of generic drug toxicity (drug withdrawal and development of severe adverse effects) and the drug-specific side effects.
Trade off between clinical benefits and harms	In relation to trade offs between benefits and harms the GDG considered both stable and unstable disease, induction of remission and maintenance of remission together with efficacy differences between drugs, long term maintenance compared to intermittent dosing, concomitant drug use, side effects, adverse events and dosing. Induction of remission is clearly important, but for most patients with stable chronic plaque psoriasis, given the long term nature of the condition and the negative impact on wellbeing, maintenance of remission is of greater importance. Long term safety is also, for the same reason, very important as systemic therapies are likely to be required over many years since none of the interventions to date have been shown to be disease modifying. The GDG agreed that the expected benefits and risks of therapy should be clearly communicated to patients and monitoring arrangements are imperative to achieve optimal outcomes and minimise risk to patients. When considering induction of remission, the ciclosporin 5mg/kg dose is more effective than the 2.5-3mg/kg dose, but is associated with greater clinically significant toxicity and drug withdrawal. The GDG agreed that dose escalation should be recommended only when a lower dose had failed or when rapid achievement of disease control necessary (such as severe/unstable disease). Studies on longer term 'maintenance' regimens were only available for ciclosporin. Low dose (1.5mg) or intermittent (twice or three times weekly dosing) showed no clinically relevant benefit in terms of disease control or toxicity, compared to placebo. Disease control was better using continuous therapy compared to intermittent 'courses' of ciclosporin for up to a year; there was no difference in toxicity although clinically relevant nephrotoxicity (i.e. >30% rise in creatinine from baseline) and new onset hypertension occurred in over 27% and 12% of all patients treated, respectively by one year. Two studies addressed intermittent (taper to withdrawal) versus continuous long term use of ciclosporin for up to 4 years but around a third of participants in each arm dropped out, so data are highly biased. The GDG noted from their clinical experience that abrupt stop of ciclosporin can cause rebound flare that may be worse than baseline disease severity although no evidence for this was found in the studies. The GDG agreed that use of continuous ciclosporin is clinically appropriate based on good efficacy, and limited toxicity, up to one year. By 18months of continuous therapy, unacceptably high rates of nephrotoxicity occur. The GDG agreed therefore that continuous treatment for longer than one year could not be routinely recommended except for patients who cannot use any other treatment

option and have severe or unstable disease. For most patients treatment with ciclosporin should be discontinued at or around one year, with repeat courses possible in the event of relapse. It was also noted that in patients who relapse rapidly, alternative treatment options should be considered given the chronicity of psoriasis and the evidence that showed that with repeated courses of ciclosporin, time to develop clinically relevant elevations of creatinine became shorter with each course.

For methotrexate, efficacy outcomes across the different studies were variable; pooled analysis indicates that methotrexate is as effective as ciclosporin by 12-16 weeks (PASI 75) although in two studies [Flytstrom, Ho] where a low initiating dose (2.5mg-7.5mg) and folic acid were used, methotrexate appeared to be less effective than ciclosporin. Risk of abnormal liver function tests and discontinuation of therapy were highest in studies when the starting dose of 15mg or greater per week (without folic acid) compared to incremental dosing from lower doses (2.5 to 10mg depending on the study). The side effect profile of methotrexate and ciclosporin differed, but there was no clinically significant difference between the two interventions with respect to overall drug withdrawal rates, serious adverse effects or relapse rates. The GDG noted from one study[325] that the improvement in DLQI was more rapid with ciclosporin than methotrexate, but by the end of the 12-week trial the DLQI scores were similar in both groups.

Whilst there was no statistically significant difference for PASI75 and time to remission when ciclosporin was compared to methotrexate, the point estimate showed a large effect size in favour of ciclosporin.

The GDG considered that for patients with stable disease requiring long term disease management and/or where there was associated psoriatic arthritis, methotrexate should be used first line based on its efficacy and safety in the short term, low cost, and the known toxicity profile of ciclosporin in the longer term. The GDG considered the evidence around dosing regimens for methotrexate insufficient to make any changes to current practice (incremental dosing, concomitant folic acid), and agreed that any benefit to starting at a therapeutic dose of methotrexate in terms of reduced time to treatment effect was outweighed by the possibility of increased risk of liver dysfunction even though this trend may have been confounded by lack of folic acid co-therapy. The GDG noted that there was variation in practice in relation to the dose and frequency of folic acid supplementation but that this was beyond the scope of the guideline and should be used in accordance with guidance in the BNF.

Data on acitretin indicated dose-related mucocutaneous toxicity occurring in the majority of people treated; efficacy appeared to be similar across all doses (25mg, 50mg, 75mg). In addition, it was noted that acitretin is teratrogenic, and needs to be discontinued for 3 years before conception in women. The GDG agreed that the clinical utility of acitretin was limited due to the uncertainty about clinical efficacy, poor tolerability and, in view of data on elevated risk of cardiovascular disease in psoriasis, associated hyperlipidaemia. In the absence of

	evidence, the clinical experience of the GDG noted that it may be helpful in a subset of patients, particularly hyperkeratotic forms of localised hand and foot psoriasis and pustular forms of psoriasis. The GDG agreed therefore that acitretin should be retained as a treatment option given the paucity of treatments available. Data on the time to maximum effect for ciclosporin indicated that across different dosages no/little further response was seen after 12 weeks, therefore, the GDG decided to use this as the time to assess response and stop treatment if the treatment is not effective. Additionally, the graphical data demonstrated that the average reduction in PASI was 50% by 4 weeks, therefore the GDG recommended that this time point should be used to assess initial response to determine whether dose escalation is required. For methotrexate, the data suggested that maximum effect was seen after 16 to 24 weeks of treatment, although the higher initial dose of 15 mg/kg in one study (Heydendael) appeared to achieve maximal response after 12 weeks of treatment. The GDG reviewed the graphical data and discussed that the time to maximum response depends on the dosing schedule and is most dependent upon the duration of treatment at the target dose when incremental dosing is used. Therefore, the GDG agreed that review of response to determine whether methotrexate should be discontinued should be performed following 3 months treatment at the target dose.
Economic considerations	No economic evidence was available to compare the cost-effectiveness of all systemic non-biological therapies – acitretin, ciclosporin and methotrexate. Two cost-utility analyses suggest that in a population with moderate to severe psoriasis, both methotrexate and ciclosporin are cost saving compared to best supportive care or no treatment. These two analyses plus a cost-minimisation analysis also indicate that methotrexate is cost saving compared to ciclosporin. Although each analysis had potentially serious limitations, largely due to a broadening evidence base since they were originally undertaken, the GDG believed that the conclusions arising from these analyses were still likely to be true. On that basis, they considered methotrexate to represent the best value for NHS resource in the population of patients for whom it is a reasonable treatment option (i.e. patients potentially requiring long term treatment and without contraindications to methotrexate). The also considered methotrexate likely to be the optimal systemic non-biological therapy in the treatment of psoriasis patients with concomitant psoriatic arthritis. For patients who cannot take methotrexate or for whom rapid control of psoriasis is the primary goal, the GDG considered short term treatment with ciclosporin to represent an efficient use of NHS resources. There was no economic evidence for the use of systemic non-biological therapies in the treatment of palmoplantar pustulosis, but the clinical evidence suggest that it is more effective than placebo/no treatment, although it carries an increased risk of hypertension. Given the ciclosporin was found to be cost saving compared to best supportive care in moderate to severe plaque

	psoriasis, the GDG considered it likely to be cost-effective in the treatment of palmoplantar pustulosis. That is, they believed that any additional costs for ciclosporin treatment in this group are likely to be justified by its additional benefits compared to no treatment. There was no economic evidence to inform the GDG of the cost-effectiveness of acitretin. Based on the clinical evidence and their clinical experience, they judged acitretin unlikely to be more cost-effective than either methotrexate or ciclosporin. Therefore, they decided it should be reserved only for patients for whom neither of these other systemic non-biological agents were suitable.
Quality of evidence	The GDG noted most of the studies addressed treatment of plaque psoriasis. Only one study addressed treatment of palmoplantar pustulosis (using ciclosporin), one nail psoriasis (Gumusel) and this was small and of low quality owing to an inadequate method of randomisation. There were no studies in children. Research recommendations were formulated for these important groups. In the absence of paediatric evidence and the importance of adequate treatment for this high need group, the GDG agreed that the recommendations on use of systemic non-biological drugs could be extrapolated to children. The available data was mostly short term (up to 16 weeks), and related to induction of remission. Trials on 'maintenance' regimens were limited to ciclosporin with no data on methotrexate or acitretin. This lack of data constitutes a major gap in evidence given that psoriasis is a chronic disease. The GDG were aware of long term registries that aim to address this shortfall in data and agreed that clinicians should talk to patients about contributing data to these registries and encourage participation whenever feasible. Further research is warranted to evaluate efficacy, optimised dosing and safety of systemic non-biological agents in psoriasis including pustular forms for both induction and remission. The following specific methodological points were noted: • The evidence mainly comprised data in adult chronic plaque psoriasis. The baseline disease severity in these studies represented the population likely to be offered treatment in the UK. • There was marked heterogeneity for all methotrexate-related efficacy outcome measures between the studies, mostly accounted for by differences in dosing regimens. Additional confounders include variation in duration of treatment and concomitant use of folic acid. • The Sandhu study (low quality) demonstrated the highest efficacy for methotrexate across all the studies and used an initial dose of 0.5mg/kg. The studies for ciclosporin vs. placebo for maintenance used different dosing schedules and definitions of relapse varied: • The Ozawa and Ohtsuki studies, while having a long (i.e.48 months) follow-up period for maintenance regimens on ciclosporin, also had very high drop-out rates so are likely to represent an underestimate

	of toxicity rates. • The Shupack and Ellis studies used a ciclosporin dose of 3mg/kg for maintenance. This dose is an induction dose. • The mean time to relapse reported in the Ellis 1995 study for 3 mg/kg/day ciclosporin group was likely to be an underestimation because follow-up was restricted to a maximum of 4 months by the protocol but most had not relapsed at this time point. Therefore, the true mean time to relapse is likely to be longer. • There was a high (30%) drop-out rate in the Colombo study and a per protocol analysis was reported for efficacy and relapse outcomes owing to the high drop-out rate (largely due to sun exposure and unwillingness to continue when improvement in the psoriasis was seen). • The RCT investigating initial dosing of ciclosporin (1.25mg or 2.5mg) [Christophers et al] allowed dose escalation in non responders and did not maintain randomisation. • The Heydendael study analysed the final PASI score by ANCOVA to take account of baseline differences. The studies for acitretin vs. placebo were small and of low quality, and included a mixture of psoriasis phenotypes including chronic plaque, guttate and pustular forms. The Lassus study, which compared different dosing regimens of acitretin, allowed concomitant use of potent steroid in all 3 trial arms so the efficacy of acitretin alone is unclear.
Other considerations	The GDG considered the clinical as well as statistical significance of the findings. The GDG agreed that: • Older people are more likely to develop nephrotoxicity with ciclosporin. • Conception plans should be taken into account when choosing which systemic non-biological therapy to use; for example ciclosporin may be relatively favoured over methotrexate in men or women of childbearing potential. • Presence of psoriatic arthritis should be considered when treating psoriasis with systemic therapy. No evidence was available on systemic therapy in children; clinical expertise within the GDG noted that a higher dose of 5mg/kg of ciclosporin is needed to be effective in children. All the systemic non-biological interventions are of variable efficacy and may lead to clinically significant toxicity including rarely, life threatening events. Supplementary topical therapy is commonly required to achieve optimal control of psoriasis with systemic non-biological therapy. This clinical opinion is supported by the evidence, as most of the studies allowed at least emollients and mild or moderate potency steroids to be used, with potent steroids allowable in some. A recommendation to encourage use of concomitant therapy was felt to be important in order to optimise outcomes.

11 Methotrexate and risk of hepatoxicity

Methotrexate is a commonly prescribed drug in psoriasis and psoriatic arthritis. It is also used as co-therapy with TNF-antagonists to improve efficacy and reduce production of neutralizing drug antibodies[2]. Aside from bone marrow suppression, which can largely be avoided with careful dosing, monitoring and avoidance of certain drug interactions[357], hepatotoxicity is the other principal side effect. Short term rises in transaminases are well recognised with methotrexate but are largely reversible, and simple to monitor. However, the insidious development of liver fibrosis and ultimately cirrhosis is of greater clinical concern given this may be irreversible, and of very significant impact. In a recent survey, 12% of UK dermatologists report experience of patients developing irreversible liver damage on long term methotrexate[358], and in one retrospective cohort study involving patients with psoriasis over a 30 year period, abnormalities in liver function tests and/or biopsy accounted for up to 25% of those who discontinued therapy[359]. Patients themselves also worry about liver damage associated with methotrexate.

There is good evidence that methotrexate use in people with psoriasis is associated with liver fibrosis, but not whether this relationship is causal. A meta-analysis of 15 cohort studies[360] including 636 patients with either psoriasis/psoriatic arthritis (n=299) or rheumatoid arthritis (n=334), indicated a significant association between methotrexate and liver pathology, and progression of histological abnormality by at least one grade in 27.9% of the cohort, and advanced pathological change (i.e.: IIIb or IV, Roenigk classification[361]) in 5%. A more recent systematic review confirmed the association but also highlighted the highly variable prevalence of fibrosis with figures ranging from between 5.7% to 71.8% when 'any stage' of fibrosis was used as the primary outcome[362]. Many of the included studies were old with poor reporting and variable histological scoring systems making these data very difficult to interpret in a modern context.

People with psoriasis may be at risk of liver disease independent of methotrexate given the elevated risk of metabolic syndrome (and by inference obesity related liver disease)[124,363-365] , alcohol related morbidity, and use of other potentially hepatotoxic drugs including arsenic (historically)[366], acitretin[367] and most recently, biological therapies[2]. Prescribing a potentially hepatotoxic drug in an at risk population is a source of clinical concern. Current guidelines on methotrexate emphasise the importance of minimising or completely avoiding alcohol when using methotrexate and this limits the clinical utility of the drug for an important proportion of people with psoriasis. In view of the common concern amongst clinicians and patients about liver fibrosis associated with methotrexate and the uncertainty about the absolute clinical risk, the GDG were interested to know whether risk factors for liver disease that are prevalent in people with psoriasis do compound the risk of methotrexate-associated liver fibrosis. If so, it might be possible to identify individuals in whom methotrexate therapy would be contra-indicated, and at the same time, reassure those at very low risk. Alternatively, if methotrexate is no more or less likely to lead to problems in those with pre-existing risk factors for liver disease, this too would be helpful to clinicians. The GDG therefore posed the following question: in people with psoriasis (all types) who are being treated with methotrexate, are there specific groups who are at high risk of hepatotoxicity?

11.1 Methodological introduction

The literature was searched for all years for studies addressing specific groups at high risk of developing hepatotoxicity when receiving methotrexate monotherapy for psoriasis. Inclusion criteria were as follows:

- Any duration of follow-up
- Sample size: N ≥ 30 (although an exception was made for the one study that looked at risk in children [24]).

- Population ≥75% people with psoriasis.
- Risk groups:
  - High cumulative dose
  - Metabolic syndrome
  - Diabetes
  - Obesity
  - Hypertension
  - Hypercholesterolaemia
  - Alcohol
  - Hepatitis B or C/infectious hepatitis
  - Pre-existing liver disease or abnormal liver function tests
- Study type: observational studies – cohort, case-control, case series.
- Data available for either the number of patients with risk factors in both those who do and do not develop hepatotoxicity or the number of patients with and without the risk factor who developed hepatotoxicity to allow comparison of the prognosis.

The outcomes considered were: hepatotoxicity – abnormal liver function tests, biopsy grade, biopsy grade progression, fatty change, periportal inflammation, fibrosis, cirrhosis.

Twenty one studies were found that addressed the question and were included in the review. 17 were case series [24,359,368-382]; 3 were cohort studies (although the cohorts were not relevant for our comparison except for the cumulative dose risk factor in one study[383])[383-385]; and 1 was a case-control study [386]. Sixteen of these studies addressed the relationship between cumulative dose of methotrexate and hepatotoxicity [359,368-371,374,375,377-385].

The studies differed in terms of their design:

- Sixteen studies[369-372,374-379,381-386] assessed whether there was an association between the presence or severity of a risk factor and the occurrence or severity of hepatotoxicity. Therefore, these data did not compare individuals with and without the risk factor.
- Ten studies[24,359,368,370,373,375,377-380] compared the numbers of participants with and without the risk factor who developed the outcome.
  - Of these, 4 studies[368,373,375,377] compared those with fibrosis or cirrhosis to those without fibrosis or cirrhosis; 3 studies[24,370,379] compared those with fibrosis or cirrhosis to those with completely normal histology; 2 studies[359,378] compared the numbers with each biopsy grade; and 3 studies compared those with normal and abnormal liver function tests[380,380,385].
- One study was conducted in children[24].

Note that no data were available the following risk groups: metabolic syndrome, hypertension and hypercholesterolaemia.

Details of the biopsy grading systems used, where available, are given for each study in the evidence tables.

Many of the studies had small samples sizes and very low numbers of people with the defined risk factors. Studies lacked clarity about whether confounding factors had been controlled for and if any liver damage was present prior to the initiation of methotrexate therapy. There is variation in the level of alcohol intake treated as a risk factor among the studies. Additionally, there may be a bias linked to timing of publication as study dates ranging from 1971 through to 2009. Patients with known risk factors will no longer be given methotrexate because practice has changed based on the

assumed risk associated with this intervention. Older publications may show a higher prevalence of hepatotoxicity because those at risk were not excluded from the therapy.

The studies were all observational and varied greatly in terms of study design and the type of data reported. It was not possible to pool the data and meta-analyse it so a narrative summary is provided. Due to the design of the studies considered, GRADE could not be used to assess quality. Therefore, quality was assessed by study using the Checklist for Prognostic studies (NICE Guidelines Manual, 2009), and studies were generally found to have methodological limitations (see Table 158). On this basis, studies were classified as low or very low quality.

Table 158: Study quality checklist

Reference	Prospective	Representative population sample	Minimal attrition bias	Prognostic factor measured appropriately	Outcomes adequately measured	Confounders accounted for	Appropriate statistical analysis	Quality
ALMEYDA1972	×	?	NA	**Alcohol:** unclear if self-report (graded as light/nil, moderate or heavy: regular average daily intake >3.5 litres beer or equivalent) **Cumulative dose**: unclear	✓ Biopsy	×[(a)]	?	Very low
AMITAL2009	×	?	NA	**Cumulative dose**: database records	✓ Liver function tests	✓ (adjusted for: age, gender, cumulative dose as a time-dependent variable)	? Unclear methods	Low
ANON1973	×	✓	NA	**Alcohol:** no – self-report (graded as none, 1-3 a week, 1-3 a day or >4 a day) **Diabetes:** from medical records **Obesity**: from medical records (unclear definition) **Cumulative dose**: no – self-report questionnaire	✓ Biopsy	× (but states matching for cumulative dose and drug schedule in analysis of alcohol intake)	✓	Very low
ASHTON1982	×	✓	NA	**Alcohol:** unclear if self-report (graded as occasional, moderate or heavy intake) **Cumulative dose**: unclear	✓ Biopsy	× (but only included those with no signs of pre-treatment fibrosis)	×	Very low
BERENDS2006	×	✓	✓ (but 16% had no BMI data)	**Yes** – all from medical records **Alcohol:** high >14 units a week **Diabetes** **Obesity**: unclear definition **Cumulative dose**	✓ Biopsy	× (but cumulative MTX dose did not affect other associations)	✓	Very low

Reference	Prospective	Representative population sample	Minimal attrition bias	Prognostic factor measured appropriately	Outcomes adequately measured	Confounders accounted for	Appropriate statistical analysis	Quality
BOFFA1995	✓	✓	?	**Alcohol:** recorded at time of biopsy as weekly units (unclear if self-report) **Cumulative dose**: calculated from clinical notes	✓ Biopsy	×	✓	Low
COLLIN2009	×	✓ Children	NA	Obesity: yes – BMI	✓ Liver function tests	×	×	Very low
KHAN2006	×	?	NA	**Cumulative dose:** medical records	✓ PIIINP and biopsy	×	?	Very low
LINDSAY2009	✓	× High proportion with PsA	✓	**Alcohol:** no – self-report **Obesity**: BMI >30 **Diabetes:** clinical assessment **Cumulative dose:** medical records	✓ Biopsy	×	✓	Very low
MALATJALIAN1996	×	?	NA	**Yes** – all from medical records **Alcohol:** ≤3 drinks/week **Obesity**: unclear definition **Diabetes** **Pre-existing liver disease**	✓ Biopsy	× (Age and years of follow-up were initially used as covariates and found to be non-significant)	✓	Very low
NEWMAN1989	×	✓	NA	**Yes** – all from medical records **Alcohol:** high >14 drinks (200g) per week **Obesity**: 40% increase above normal weight **Diabetes** **Cumulative dose**	✓ Biopsy	?	✓	Very low
NYFORS1976	×	✓	NA	**Alcohol:** no – self-report questionnaire (graded as occasional,	✓	?	✓	Very low

Reference	Prospective	Representative population sample	Minimal attrition bias	Prognostic factor measured appropriately	Outcomes adequately measured	Confounders accounted for	Appropriate statistical analysis	Quality
				1-3 a week, 1-3 a day or >3 a day) **Pre-existing liver disease**: no – self-report questionnaire **Cumulative dose**: unclear	Biopsy	Multivariate analysis: pre-MTX liver biopsy, MTX cumulative dose, alcohol intake, age and obesity (but not clear if these confounders were controlled for when assessing the impact of individual risk factors)		
NYFORS1977	×	✓	NA	**Alcohol:** no – self-report questionnaire (graded as occasional, 1-3 a week, 1-3 a day or >3 a day) **Obesity**: unclear definition **Cumulative dose**: unclear	✓ Biopsy	×	✓	Very low
OCONNOR1989	×	?	NA	**Alcohol:** unclear if self-report (categorised as yes or no: yes means >1 drink/day) **Obesity**: unclear definition (from medical records)	✓ Biopsy	? (but only included those with no signs of pre-treatment liver abnormalities)	?	Very low
REESE1974	✓	?	?	**Alcohol:** self-report (classified as no to minimal intake (1-2 oz hard liquor or equivalent); or moderate-to-excessive intake (regular daily intake or sporadic heavy use)) **Cumulative dose**: unclear	✓ Biopsy	✓ (adjusted for: alcohol, MTX dose, MTX duration)	✓	Low
ROENIGK1971	×	✓	NA	**Alcohol:** unclear if self-report (categorised as no intake; 1 drink/week; 1 drink/day; >1 drink/day; ≥1 pints of hard liquor/day) **Obesity**: unclear definition	✓ Biopsy	×	×	Very low

Reference	Prospective	Representative population sample	Minimal attrition bias	Prognostic factor measured appropriately	Outcomes adequately measured	Confounders accounted for	Appropriate statistical analysis	Quality
				Diabetes: laboratory evidence **Cumulative dose:** unclear				
ROSENBERG2007	×	✓	NA	**Yes** – all from medical records **Alcohol:** high >30g per day **Diabetes:** yes – fasting blood glucose >6.0 mmol/l or blood glucose >11 mmol 2 h after intake of 75 g glucose **Hepatitis B/C**	✓ Biopsy	×	✓	Very low
TOBIAS1973	×	× Severe psoriasis (≥80% BSA)	NA	**Alcohol:** unclear if self-report (categorised as 0, 28–85, or >88 g/week) **Obesity**: unclear definition **Diabetes:** medical records **Cumulative dose:** unclear	✓ Biopsy	×	×	Very low
VANDOORENGREEBE1994	×	✓	NA	**Cumulative dose:** medical records	✓ Biopsy	×	×	Very low
WOLLINA2001	×	× Young and high proportion with PsA	NA	**Cumulative dose:** medical records	✓ Liver function tests	×	✓	Very low
ZACHARIAE1975	?	?	?	**Alcohol:** self-report (high alcohol intake >4 drinks per day)	✓ Biopsy	×	?	Very low

×: No
✓: Yes
?: Unclear
NA: not applicable

(a) Differences between those with and without liver damage were noted: Those who developed fibrosis or cirrhosis had significantly greater mean cumulative dose of MTX than those with normal biopsies (p=0.05); no statistically significant differences in duration of treatment between those with and without abnormal biopsies; the 3 patients with cirrhosis received MTX for a mean of 52 months vs 33 months for those with normal biopsies; the 3 patients with cirrhosis had all received MTX by the daily oral regime, but fibrosis was found with approximately equal frequency in all 3 regimes

11.2 Adults

11.2.1 Risk factor 1: Alcohol

11.2.1.1 Summary of included studies and results

Table 159: Included studies assessing alcohol as a risk factor for hepatotoxicity

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Alcohol							
Rosenberg et al (2007) [373] Retrospective case series	71	>30g daily N=9 Note: 1 standard drink is approx. 10g pure alcohol	Up to 28 years	51/49	Median: 48	Range: 0-17.2 g	**Alcohol increased the risk of fibrosis (Kleiner and Brunt scoring)** • 9/9 (100%) people with excess alcohol consumption developed fibrosis vs 41/62 (66%) without excess alcohol consumption **Alcohol did not increase the risk of severe fibrosis (fibrosis severity scored by an unnamed 0-4 system similar to Scheuer)** • 2/9 (22%) of people with excess alcohol consumption developed severe liver fibrosis vs 11/62 (18%) without excess alcohol consumption (NS)
Newman et al (1989) [371] Case series and within-group comparison	168	High intake: >200g pure alcohol per week N=8 or Moderate intake: 1-7 fl. oz (30-200g) pure alcohol per week	Not reported	52/48	Mean: 47.7	Median monthly MTX dose before biopsy among 86 patients with MTX treatment before biopsy 67.3 (7.5-205.6) mg	**Alcohol consumption (high or moderate) not a risk factor for hepatotoxicity (Roenigk grade)**

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
		N not given					
Zachariae et al (1975) [386] Case control	139	High intake: >4 drinks / day (approximately >40 g pure alcohol) N=10 Moderate intake: 1-3 drinks/day (approximately 10-30 g pure alcohol) N=10	Not reported	Not reported	Not reported	Mean: 936 mg	**Alcohol consumption not a risk factor for cirrhosis and fibrosis (unnamed 1-4 scale), or for the severity of periportal inflammation** • 6/76 (7.9%) with low alcohol consumption developed cirrhosis; 0/20 with moderate or high alcohol consumption developed cirrhosis • No significant difference between high and low alcohol consumers for fibrosis • No apparent difference in grade of periportal inflammation between low and high alcohol consumers
Reese et al (1974) [383] Prospective cohort study	70 (50% treated)	Regular daily intake or sporadic heavy use N=19 (of the 35 treated)	Duration of treatment: 0.5-8 years	Not reported	Range: 22-69	Range: 100-5000 mg	**Alcohol consumption increases risk of mild hepatotoxicity (mostly fatty change; unnamed 0-4 scale)** • Statistically significant effect of alcohol intake on biopsy histology ($p<0.001$) mostly due to fatty change and, to a lesser extent, fibrosis **Level of alcohol intake may not be a risk factor for severe fibrosis and cirrhosis** • 1/16 with no-to-minimal intake had significant fibrosis vs 1/19 moderate-to-excessive drinkers • 1/16 with no-to-minimal intake had cirrhosis vs 0/19 moderate-to-excessive drinkers **Level of alcohol intake may be a risk factor for abnormal liver histology** • 6/16 (37.5%) with no-to-minimal intake had normal histology vs 1/19 (5.3%) moderate-to-excessive drinkers

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Boffa et al (1995) [369] Prospective case series	49	Not reported (continuous data) – association of units/wk with histology score ***Note:*** *gives alcohol units/week pre-MTX and at time of last biopsy*	Mean time between first and last biopsies: 225 weeks (range: 60-460 weeks) Mean duration of treatment 275 (26-738) weeks	61/39	Mean (at last biopsy): 54.8	Mean at first biopsy: 2743 mg (range: 315-10,024 mg) plus an average of 2362 mg during FU	**Alcohol consumption not a risk factor for hepatotoxicity (histology score; unnamed 1-5 scale)** • Histology score at end point greater in those with lowest alcohol consumption both during and before MTX ***Note:*** *those with the greatest decrease in alcohol intake between pre-MTX and last biopsy showed the lowest histology score*
Almeyda et al (1972) [384] Retrospective cohort	42	Regular daily intake >3.5 litres beer or equivalent (approximately >10 g pure alcohol) N=7	Treatment duration: 3-80 weeks	Not reported (58/42 for total sample)	Mean 55 (range: 21-77)	Not reported	**Alcohol consumption may be a risk factor for cirrhosis and abnormal liver histology, but not fibrosis (unnamed 0-3 scale)** • 3/3 (100%) with cirrhosis had heavy alcohol intake • 0/12 (0%) with fibrosis had heavy alcohol intake • 2/10 (20%) with minor liver abnormalities had heavy alcohol intake • 2/17 (12%) with normal histology had heavy alcohol intake
Ashton et al (1982) [368] Retrospective case series	38	>100 g/week N=8	Mean treatment duration: 32.7 months (range: 12-102 months)	45/55	Mean: 53 (range: 29-81)	Mean: 1928 mg (range: 800-5500 mg)	**Alcohol consumption is a risk factor for fibrosis and cirrhosis (unnamed scale)** • Of 8 heavy drinkers, 4 developed fibrosis or cirrhosis (50%) • Of 30 non-heavy drinkers 5 developed fibrosis or cirrhosis (16.7%)
Nyfors et al (1977) [370] Retrospective case series	160 (92 in part A and 68 in part B)	*See table in results column Stratified as*	Part A – mean treatment duration: 52	A – 50/50 B – 49/51	Mean: 57	A – Mean: 2287 mg (range: 50-5075 mg) B – Mean at time of last biopsy: 3940 mg	**Alcohol consumption is a risk factor for fibrosis and cirrhosis (unnamed scale)** • A – Those who developed fibrosis or cirrhosis consumed statistically more alcohol **during** therapy

<table>
<tr><th>Study</th><th>N</th><th>N with risk factor</th><th>Follow up</th><th>Gender (M/F%)</th><th>Age (years)</th><th>Treatment (cumulative dose)</th><th>Results</th></tr>
<tr><td></td><td></td><td>approximately 10-30g a week; 10-30 g a day and >30g a day</td><td>months (range: 2-105 months)</td><td></td><td></td><td>(range: 325-8355 mg)</td><td>than those with normal histology
– There was also a modest apparent effect for increased alcohol consumption prior to MTX being linked to increased risk of developing fibrosis or cirrhosis
• B – Those who developed cirrhosis consumed statistically more alcohol during therapy than those with normal histology (p=0.041)
– There was also a modest apparent effect for increased alcohol consumption prior to MTX being linked to increased risk of developing fibrosis or cirrhosis
<table><tr><th>Study</th><th>Alcohol intake</th><th>Pre-MTX</th><th>During MTX</th></tr><tr><td>Part A</td><td>Occasional</td><td>40</td><td>44</td></tr><tr><td></td><td>1-3 a week</td><td>14</td><td>33</td></tr><tr><td></td><td>1-3 a day</td><td>23</td><td>19</td></tr><tr><td></td><td>>3 a day</td><td>15</td><td>6</td></tr><tr><td>Part B</td><td>Occasional</td><td>27</td><td>28</td></tr><tr><td></td><td>1-3 a week</td><td>20</td><td>26</td></tr><tr><td></td><td>1-3 a day</td><td>18</td><td>11</td></tr><tr><td></td><td>>3 a day</td><td>3</td><td>3</td></tr></table></td></tr>
<tr><td>O’Connor et al (1989) [372]
Retrospective case series</td><td>78</td><td>>1 drink (10g)/day</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td>Alcohol consumption not a significant risk factor for fibrosis and cirrhosis (composite of Roenigk biopsy grades III-IV)</td></tr>
<tr><td>No authors listed (1973) [374]
Case series and within-group analysis</td><td>338</td><td>1-3 drinks (10-30g)/wk N=190
1-3 drinks (10-30g)/day</td><td>Mean treatment duration: 2.8±2.0 years</td><td>57/43</td><td>Mean: 46.5</td><td>Mean: 1.84 g</td><td>Alcohol consumption is a risk factor for hepatotoxicity (periportal inflammation, fibrosis and cirrhosis; unnamed scale)
• Increasing alcohol intake significantly correlated with presence of hepatotoxicity</td></tr>
</table>

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
		N=79 ≥4 drinks (≥40g)/day N=68					
Berends et al (2006) [359] Retrospective chart review	125	Any consumption N=61 >14 units (140 g)/wk N=11	Median treatment duration: 228 weeks (range: 16-1763)	54/46	Mean: 45.0	Median: 2113 mg (range: 180-20,235)	**Alcohol consumption is not a risk factor for biopsy grade progression (Roenigk score)** • High alcohol use did not lead to progression to higher Roenigk score at earlier cumulative MTX dose **Alcohol use may be a risk factor for fibrosis and cirrhosis, but not for abnormal histology** • 5/62 (8%) of those who used alcohol vs 0/34 of those with no risk factors reached grades IIIa-IV • 49/62 (79%) of those who used alcohol vs 29/34 (85%) of those with no risk factors had grade I
Malatjalian et al (1996) [376] Retrospective case series	104	1-3 drinks (10-30g) /week N=20	Mean while on MTX: 3.8 years	57/43	Mean: 42.8 (range:16-71)	Not reported	**Alcohol consumption is not a risk factor for hepatotoxicity (biopsy Roenigk grade)** • Increased biopsy grade progression not associated with alcohol use (p=0.93)
Tobias et al (1973) [377] Case series	88 (69 treated)	0 g/week N=41 28–85 g/week N=16 >88 g/week N=12	Duration of treatment: 0.1-10 years	50.8/49.2	Mean 48.3 (for total group)	Range: 60-9600 mg	**Alcohol consumption is a risk factor for fatty change** • Increased alcohol consumption associated with increased fat **Alcohol consumption may be a risk factor for cirrhosis, significant fibrosis and abnormal histology, but may not be for slight fibrosis (unnamed 1-4 grading scale):** Alcohol intake: Hepatotoxicity — Cirrhosis; Marked-to-moderate fibrosis; Slight fibrosis; No fibrosis

<table>
<tr><th>Study</th><th>N</th><th>N with risk factor</th><th>Follow up</th><th>Gender (M/F%)</th><th>Age (years)</th><th>Treatment (cumulative dose)</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>0 g/week</td><td>2 (4.9%)</td><td>6 (14.6%)</td><td>6 (14.6%)</td><td>27 (65.9%)</td></tr>
<tr><td>28–85 g/week</td><td>1 (20%)</td><td>4 (25.0%)</td><td>2 (12.5%)</td><td>9 (56.3%)</td></tr>
<tr><td>>85 g/week</td><td>2 (16.7%)</td><td>3 (25.0%)</td><td>1 (8.3%)</td><td>6 (50.0%)</td></tr>
</table>
</td></tr>
<tr><td>Lindsay et al (2009) [375]
Prospective case series</td><td>54 (47 with both skin and joint involvement)</td><td>Excessive intake (> recommended weekly intake UK)
N=9</td><td>Mean duration of treatment: 6.9 years</td><td>Not reported</td><td>Mean 54.4</td><td>Mean: 4396 mg (range: 1020-19,657 mg)</td><td>Alcohol is not a risk factor for fibrosis (Roenigk grade 3)
• Those who did not develop fibrosis consumed significantly more units of alcohol per week than those who did develop fibrosis (p=0.02)</td></tr>
<tr><td>Roenigk et al (1971) [378]

Retrospective cohort study</td><td>50 (37 treated)</td><td>Moderate to heavy: ≥1 drink (10g)/day
N=14

Minimal-to-no: ≥1 drink (10g)/wk
N=27</td><td>Not reported</td><td>56.8/43.2</td><td>Post-MTX group: mean 45</td><td>Range: 25-10,000 mg</td><td>Alcohol is not a risk factor for biopsy grade
• Poor correlation between the severity of abnormality on liver biopsy and level of alcohol consumption
• Alcohol may be a risk factor for mild abnormal biopsy histology, but not for severe fatty change fibrosis and cirrhosis (arbitrary 1-5 scale)
<table>
<tr><th rowspan="2">Alcohol intake</th><th colspan="5">Liver biopsy classification (%)</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Minimal-to-non</td><td>25.9</td><td>22.2</td><td>29.6</td><td>7.4</td><td>14.8</td></tr>
<tr><td>Moderate-to-heavy</td><td>7.1</td><td>50.0</td><td>21.4</td><td>7.1</td><td>14.3</td></tr>
</table>
</td></tr>
<tr><td>Nyfors et al (1976) [379]
Case series</td><td>88</td><td>See table in results column Stratified as approximatel</td><td>Average duration of treatment 26 months</td><td>47.7/52.3</td><td>Mean 50 (range: 21-78)</td><td>Mean 1733 mg (range: 175-4590 mg)</td><td>Alcohol is not a risk factor for fibrosis/cirrhosis (unnamed grading scale)
• The 11 patients who developed fibrosis or cirrhosis did not have significantly higher alcohol intake during therapy (p>0.05) than the 28 whose liver</td></tr>
</table>

<table>
<tr><th>Study</th><th>N</th><th>N with risk factor</th><th>Follow up</th><th>Gender (M/F%)</th><th>Age (years)</th><th>Treatment (cumulative dose)</th><th>Results</th></tr>
<tr><td></td><td></td><td>y 10-30g a week; 10-30 g a day and >30g a day</td><td></td><td></td><td></td><td></td><td>pathology remained normal
• There was also a modest apparent effect for increased alcohol consumption prior to MTX being linked to increased risk of developing fibrosis or cirrhosis
Alcohol may be a risk factor for cirrhosis (unnamed grading scale)
• The three participants who had cirrhosis diagnosed within the first 3 years of MTX therapy had relatively low cumulative MTX doses but an intake of >4 alcoholic drinks a day
<table>
<tr><th>Alcohol intake</th><th>Pre-MTX (n)</th><th>During MTX (n)</th></tr>
<tr><td>Occasional</td><td>46</td><td>56</td></tr>
<tr><td>1-3 a week</td><td>12</td><td>23</td></tr>
<tr><td>1-3 a day</td><td>22</td><td>6</td></tr>
<tr><td>>3 a day</td><td>8</td><td>3</td></tr>
</table></td></tr>
</table>

1

11.2.112 Evidence statements: Alcohol

There was inconsistency between studies assessing the risk of hepatotoxicity associated with alcohol intake in people with psoriasis taking methotrexate. This was true for all outcomes:

- Cirrhosis
  - 2 studies demonstrated a statistically significantly increased risk associated with alcohol consumption [406 participants; very low quality evidence] [370†374]
  - 2 studies suggested an apparent increase in risk associated with alcohol consumption [2 studies; 111 participants; very low quality evidence][384*377†] and one study suggested an apparent link based on post hoc data for cirrhosis [88 participants; very low quality evidence][379]
  - 1 study demonstrated no statistically significantly increased risk associated with alcohol consumption [139 participants; very low quality evidence] [386]
  - 3 studies suggested no apparent increase in risk associated with alcohol consumption [211 participants; low to very low quality evidence][378,383,386]

- Composite outcome of cirrhosis and fibrosis
  - 1 study demonstrated a statistically significantly increased risk associated with alcohol consumption [92 participants; very low quality evidence] [370†]
  - 5 studies suggested an apparent increase in risk associated with alcohol consumption [411 participants; very low quality evidence] [368*359,370,379]
  - 2 studies demonstrated no statistically significantly increased risk associated with alcohol consumption [166 participants; very low quality evidence] [372,379*]
- Fibrosis
  - 1 study demonstrated a statistically significantly increased risk associated with alcohol consumption [338 participants; very low quality evidence] [374]
  - 2 studies suggested an apparent increase in risk associated with alcohol consumption; one reported significant fibrosis only [1 study; 69 participants; very low quality evidence][377†] while one reported all fibrosis [1 study; 71 participants; very low quality evidence][373*]
  - 3 studies demonstrated no statistically significantly increased risk associated with alcohol consumption; 2 reported on all fibrosis [2 studies; 193 participants; very low quality evidence] [375,386*], while another reported on severe fibrosis only [1 study; 71 participants; very low quality evidence] [373*]
  - 7 studies suggested no apparent increase in risk associated with alcohol consumption; 1 reported on significant fibrosis only [1 study; 35 participants; low quality evidence] [383], another two on all fibrosis [2 studies; 79 participants; very low quality evidence][384*378] and one only on slight fibrosis [1 study; 69 participants; very low quality evidence][377†]
- Fatty change
  - 2 studies suggested an apparent increase in risk associated with alcohol consumption; one reported all fatty change [1 study; 69 participants; very low quality evidence] [377†], while another reported only mild fatty change [1 study; 37 participants; very low quality evidence][378*]
  - 1 study suggested no apparent increase in risk associated with alcohol consumption for significant fatty change [37 participants; very low quality evidence][378]
- Periportal inflammation
  - 1 study demonstrated a statistically significantly increased risk associated with alcohol consumption [338 participants; very low quality evidence] [374]

- 1 study suggested an apparent increase in risk associated with alcohol consumption [139 participants; very low quality evidence][386]

- Biopsy grade
  - 1 study demonstrated a statistically significantly increased risk associated with alcohol consumption [35 participants; low quality evidence] [383]
  - 2 studies demonstrated no statistically significantly increased risk associated with alcohol consumption; one assessed biopsy grade [1 study; 168 participants; very low quality evidence] [371] and the other biopsy grade progression [1 study; 104 participants; very low quality evidence] [376]
  - 3 studies suggested no apparent increase in risk associated with alcohol consumption; two assessed biopsy grade [2 studies; 86 participants; low to very low quality evidence][369,378] while another assessed biopsy grade progression [1 study; 125 participants; very low quality evidence][359]
- Abnormal histology
  - 4 studies suggested an apparent increase in risk associated with alcohol consumption [183 participants; low to very low quality evidence][383,384*377†378*]
  - 1 study suggested no apparent increase in risk associated with alcohol consumption [125 participants; very low quality evidence][359]

*In these studies the number of participants with alcohol intake was <10.

†This outcome is based on alcohol consumption during MTX therapy.

11.2.12 Risk Factor 2: Obesity

11.2.221 Summary of included studies and results

3 **Table 160: Included studies assessing obesity as a risk factor for hepatotoxicity**

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Obesity							
Newman et al (1989) [371] Case series	168	67		52/48	Mean: 47.7	Median monthly MTX dose before biopsy among 86 patients with MTX treatment before biopsy 67.3 (7.5-205.6) mg	**Obesity is a risk factor for hepatotoxicity (Roenigk grade)** • Significant association between biopsy grade and obesity (p=0.003)
Nyfors et al (1977) [370] Retrospective case series	160 (92 in part A and 68 in part B)	Part A – 29 Part B – 23	Part A – mean treatment duration: 52 months (range: 2-105 months)	A – 50/50 B – 49/51	Mean: 57	A – Mean: 2287 mg (range: 50-5075 mg) B – Mean at time of last biopsy: 3940 mg (range: 325-8355 mg)	**Obesity is not a risk factor for fibrosis/cirrhosis (unnamed scale)** • A – No significant difference in number of patients with obesity between those with and without fibrosis/cirrhosis **Obesity is a risk factor for cirrhosis** • B – Significantly more patients with cirrhosis were obese than those without cirrhosis (p=0.033)
O'Connor et al (1989) [372] Retrospective case series (diagnostic)	78	Not reported	Not reported	Not reported	Not reported	Not reported	**Obesity not a risk factor for fibrosis and cirrhosis (composite of Roenigk biopsy grades III-IV)**
No authors listed(1973) [374] Case series and within-group analysis	338	108	Mean treatment duration: 2.8±2.0 years	57/43	Mean: 46.5	Mean: 1.84 g	**Obesity is a risk factor for mild hepatotoxicity (fatty liver; unnamed grading system)** • Obesity significantly correlated with presence of mild hepatotoxicity
Berends et al (2006) [359]	125	Not reported	Median	54/46	Mean: 45.0	Median: 2113 mg	**Obesity is a risk factor for hepatotoxicity**

<table>
<tr><th>Study</th><th>N</th><th>N with risk factor</th><th>Follow up</th><th>Gender (M/F%)</th><th>Age (years)</th><th>Treatment (cumulative dose)</th><th>Results</th></tr>
<tr><td>Retrospective chart review</td><td></td><td>(gives numbers of overweight)</td><td>treatment duration: 228 weeks (range: 16-1763)</td><td></td><td></td><td>(range: 180-20,235)</td><td>(Roenigk score)
• Obesity led to progression to higher Roenigk score at earlier cumulative MTX dose</td></tr>
<tr><td>Malatjalian et al (1996) [376]

Retrospective case series</td><td>104</td><td>14</td><td>Mean while on MTX: 3.8 years</td><td>57/43</td><td>Mean: 42.8 (range:16-71)</td><td>Not reported</td><td>Obesity may be a risk factor for hepatotoxicity (biopsy Roenigk grade; composite of fibrosis and cirrhosis)
• Increased biopsy grade progression is associated with obesity (p=0.001)
• Progression to final biopsy grades IIIB (severe fibrosis) and IV (cirrhosis) is not associated with obesity (p=0.12)</td></tr>
<tr><td>Tobias et al (1973) [377]
Case series</td><td>88 (69 treated)</td><td>1</td><td>Duration of treatment: 0.1-10 years</td><td>50.8/49.2</td><td>Mean 48.3 (for total group)</td><td>Range: 60-9600 mg</td><td>Unclear evidence (unnamed 1-4 scale)
• Only one obese patient in the treatment group: developed slight fibrosis</td></tr>
<tr><td>Lindsay et al (2009) [375]
Prospective case series</td><td>54 (47 with both skin and joint involvement)</td><td>15</td><td>Mean duration of treatment: 6.9 years</td><td>Not reported</td><td>Mean 54.4</td><td>Mean: 4396 mg (range: 1020-19,657 mg)</td><td>Obesity is not a risk factor for fibrosis (Roenigk grade 3)
• No significant difference between the BMI of those who do and do not develop fibrosis</td></tr>
<tr><td>Roenigk et al (1971) [378]
Retrospective cohort study</td><td>50 (37 treated)</td><td>18</td><td>Not reported</td><td>56.8/43.2</td><td>Post-MTX group: mean 45</td><td>Range: 25-10,000 mg</td><td>Obesity may be a risk factor for fibrosis, severe fatty change and abnormal histology (unnamed grading system), but not for cirrhosis or mild fatty change
<table>
<tr><th rowspan="2">Obesity</th><th colspan="5">Liver biopsy classification (%)</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>No.</td><td>26.3</td><td>36.8</td><td>21.1</td><td>0</td><td>15.8</td></tr>
<tr><td>Yes</td><td>11.1</td><td>22.2</td><td>38.0</td><td>16.7</td><td>11.1</td></tr>
</table></td></tr>
</table>

11.2.212 Evidence statements: Obesity

There was inconsistency between studies assessing the risk of hepatotoxicity associated with obesity in people with psoriasis taking methotrexate. This was true for the majority of outcomes as outlined below:

- Cirrhosis
  - 1 study demonstrated a statistically significantly increased risk associated with obesity [68 participants; very low quality evidence][370]
  - 1 study suggested no apparent increased risk associated with obesity [1 study; 37 participants; very low quality evidence][378]
- Composite outcome of cirrhosis and fibrosis
  - 2 studies demonstrated no statistically significantly increased risk associated with obesity [170 participants; very low quality evidence][370,372†]; another study demonstrated no statistically significantly increased risk associated with obesity for progression to severe fibrosis or cirrhosis [1 study; 104 participants; very low quality evidence][376]
- Fibrosis
  - 1 study suggested an apparent increased risk associated with obesity [37 participants; very low quality evidence][378]
  - 1 study demonstrated no statistically significantly increased risk associated with obesity [1 study; 54 participants; very low quality evidence][375]
- Fatty change
  - 1 study demonstrated a statistically significantly increased risk associated with obesity [338 participants; very low quality evidence][374]
  - 1 study suggested an apparent increased risk associated with obesity for severe fatty change but not for mild fatty change [1 study; 37 participants; very low quality evidence][378]
- Biopsy grade
  - 2 studies demonstrated a statistically significantly increased risk associated with obesity; one assessed biopsy grade [168 participants; very low quality evidence][371] and the other progression to higher biopsy grade [1 study; 104 participants; very low quality evidence][376]
  - 1 study suggested an apparent increased risk associated with obesity for progression to higher biopsy grade [1 study; 125 participants; very low quality evidence][359]†
- Abnormal histology
  - 1 study suggested an apparent increased risk associated with obesity [37 participants; very low quality evidence][378]

One study[377] showed unclear evidence for any link between obesity and hepatotoxicity because only one participant was obese.

†In these two studies the total number of participants with obesity was unclear.

11.2.3 Risk factor 3: Diabetes

11.2.3.1 Summary of included studies and results

Table 161: Included studies assessing diabetes as a risk factor for hepatotoxicity

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Diabetes							
Rosenberg et al (2007) [373] Retrospective case series	71	3	Up to 28 years	51/49	Median at start of treatment: 48	Range: 0-17.2 g	**Diabetes is a risk factor for fibrosis and severe fibrosis (Kleiner and Brunt scoring; fibrosis severity scored by an unnamed 0-4 system similar to Scheuer)** • 100% of those with diabetes developed fibrosis vs 52% of those without • 57% of those with diabetes developed severe liver fibrosis vs 14% of those without (p = 0.003)
Newman et al (1989) [371] Case series (prognosis)	168	16		52/48	Mean: 47.7	Median monthly MTX dose before biopsy among 86 patients with MTX treatment before biopsy 67.3 (7.5-205.6) mg	**Diabetes not a risk factor for hepatotoxicity (Roenigk grade)**
No authors listed(1973) [374] Case series and within-group analysis	338	33	Mean treatment duration: 2.8±2.0 years	57/43	Mean: 46.5	Mean: 1.84 g	**Diabetes is a risk factor for fatty liver and fibrosis (unnamed scale)** • Significant difference between those with and without diabetes in terms of mean fatty liver and fibrosis grades **Diabetes is not a risk factor for cirrhosis or periportal inflammation (unnamed scale)**

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
							• No significant difference between those with and without diabetes in terms of mean cirrhosis or periportal inflammation grade
Berends et al (2006) [359] Retrospective chart review	125	9	Median treatment duration: 228 weeks (range: 16-1763)	54/46	Mean: 45.0	Median: 2113 mg (range: 180-20,235)	**Diabetes is a risk factor for biopsy grade progression (Roenigk score)** • Diabetes led to progression to higher Roenigk score at earlier cumulative MTX dose **Diabetes may be a risk factor for fibrosis and cirrhosis and any abnormal biopsy histology** • 2/9 (22%) diabetics vs 0/34 (0%) of those with no risk factors reached grades IIIa-IV • 6/9 (67%) diabetics vs 29/34 (85%) of those with no risk factors had grade I
Malatjalian et al (1996) [376] Retrospective case series	104	2	Mean while on MTX: 3.8 years	57/43	Mean: 42.8 (range:16-71)	Not reported	**Diabetes may be a risk factor for hepatotoxicity** (link not found for biopsy Roenigk grade progression; link found for composite outcome of fibrosis and cirrhosis) • Increased biopsy grade progression is not associated with diabetes (p=0.42) • Progression to final biopsy grades IIIB (severe fibrosis) and IV (cirrhosis) is associated with diabetes (p=0.02)
Tobias et al (1973) [377] Case series	88 (69 treated)	2	Duration of treatment: 0.1-10 years	50.8/49.2	Mean 48.3 (for total group)	Range: 60-9600 mg	**Unclear evidence (unnamed scale)** • Only two diabetic patients in the treatment group: one developed moderate fibrosis and the other developed slight fibrosis

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Lindsay et al (2009) [375] Prospective case series	54 (47 with both skin and joint involvement)	4	Mean duration of treatment: 6.59 years	Not reported	Mean 54.4	Mean: 4396 mg (range: 1020-19,657 mg)	**Diabetes is not a risk factor for fibrosis (Roenigk grade 3)** • No significant difference between the number of diabetics who did and did not develop fibrosis
Roenigk et al (1971) [378] Retrospective cohort study	50 (37 treated)	6	Not reported	56.8/43.2	Post-MTX group: mean 45	Range: 25-10,000 mg	**Diabetes may be a risk factor for hepatotoxicity (abnormal biopsy histology; unnamed scale)** • Of 6 diabetics 5 had liver damage, but all of these 5 were also obese and had relatively high cumulative MTX dose

1

11.2.312 Evidence statements: Diabetes

There was inconsistency between studies assessing the risk of hepatotoxicity associated with diabetes in people with psoriasis taking methotrexate. This was true for the majority of outcomes as outlined below:

- Cirrhosis
  - 1 study demonstrated no statistically significantly increased risk associated with diabetes [338 participants; very low quality evidence][374]

- Composite of severe fibrosis and cirrhosis
  - 1 study demonstrated a statistically significantly increased risk associated with diabetes [104 participants; very low quality evidence][376*]
  - 1 study suggested an apparent increased risk associated with diabetes [1 study; 125 participants; very low quality evidence][359]*
- Fibrosis
  - 2 studies demonstrated a statistically significantly increased risk associated with diabetes; one reported only severe fibrosis [1 study; 71 participants; very low quality evidence][373*] while the other reported any fibrosis [1 study; 338 participants; very low quality evidence][374]
  - 1 study suggested an apparent increased risk associated with diabetes [71 participants; very low quality evidence][373]*
  - 1 study demonstrated no statistically significantly increased risk associated with diabetes [1 study; 54 participants; very low quality evidence][375]*
- Fatty liver
  - 1 study demonstrated a statistically significantly increased risk associated with diabetes [338 participants; very low quality evidence][374]
- Periportal inflammation
  - 1 study demonstrated no statistically significantly increased risk associated with diabetes [338 participants; very low quality evidence][374]
- Biopsy grade
  - 2 studies suggested an apparent increased risk associated with diabetes; one assessed biopsy grade [1 study; 37 participants; very low quality evidence][378*] while the other assessed biopsy grade progression [1 study; 125 participants; very low quality evidence][359*]
  - 2 studies demonstrated no statistically significantly increased risk associated with diabetes; one assessed biopsy grade [1 study; 168 participants; very low quality evidence][371] while the other assessed progression to higher biopsy grade [1 study; 104 participants; very low quality evidence][376]*
- Abnormal histology
  - 1 study suggested an apparent increased risk associated with diabetes [125 participants; very low quality evidence][359*]

One study[377*] showed unclear evidence for any link between diabetes and hepatotoxicity.

*These studies had fewer that 10 participants with diabetes.

11.2.4 Risk Factor 4: Viral hepatitis

11.2.4.1 Summary of included studies and results

Table 162: Included study assessing hepatitis as a risk factor for hepatotoxicity

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Hepatitis							
Rosenberg et al (2007) [373] Retrospective case series	71	2	Up to 28 years	51/49	Median at start of treatment: 48	Range: 0-17.2 g	**Increased risk of fibrosis (Kleiner and Brunt scoring) in people with viral hepatitis** • 100% of those with viral hepatitis developed fibrosis • 33% of those with viral hepatitis developed severe liver fibrosis (fibrosis severity scored by an unnamed 0-4 system similar to Scheuer)

11.2.4.2 Evidence statement: Viral hepatitis

One study showed an apparent link between viral hepatitis and hepatotoxicity. The outcome was:

- Fibrosis [1 study; 71 participants; very low quality evidence][373*]

* This study had only 2 participants with viral hepatitis.

11.2.5 Risk Factor 5: Pre-existing liver disease

11.2.5.1 Summary of included studies and results

Table 163: Included studies assessing pre-existing liver disease as a risk factor for hepatotoxicity

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Pre-existing liver disease							
Rosenberg et al (2007) [373] Retrospective case series	71	Not reported	Up to 28 years	51/49	Median at start of treatment: 48	Range: 0-17.2 g	**Serum ALT, AST and γGT before treatment did not predict fibrosis (Kleiner and Brunt scoring)**
Malatjalian et al (1996) [376] Retrospective case series	104	8	Mean while on MTX: 3.8 years	57/43	Mean: 42.8 (range:16-71)	Not reported	**Pre-existing liver pathology may be a risk factor for severe hepatotoxicity (composite of severe fibrosis and cirrhosis)** • 62.5% of patients with pre-MTX grade IIIA (periportal fibrosis) liver biopsies (5/8) progressed to bridging fibrosis or cirrhosis
Nyfors et al (1976) [379] Case series	88	8	Average duration of treatment 26 months	47.7/52.3	Mean 50 (range: 21-78)	Mean 1733 mg (range: 175-4590 mg)	**Pre-existing liver pathology may not be a risk factor for fibrosis/cirrhosis (unnamed grading system)** • Cirrhosis and fibrosis developed more frequently in patients with abnormal (8/41) than with normal (3/47) pre-MTX biopsies (p = 0.062)

Initial grade	Final grade				
	I	II	IIIA	IIIB	IV
I	37	10	17	14	2
II	3	2	8	3	0
IIIA	0	1	2	4	1

11.2.512 Evidence statements: Pre-existing liver disease

There was inconsistency between the two studies assessing the risk of hepatotoxicity associated with pre-existing liver disease in people with psoriasis taking methotrexate for one outcome:

- Composite outcome of severe fibrosis and cirrhosis
  - 1 study suggested an apparent increased risk associated with pre-existing periportal fibrosis [1 study; 104 participants; very low quality evidence][376*]
  - 1 study demonstrated no statistically significantly increased risk associated with completely normal pre-treatment biopsy compared with those with any degree of abnormality on liver biopsy pre-treatment [1 study; 88 participants; very low quality evidence][379*]

Only one study reported on the other available outcome:

- Fibrosis
  - 1 study demonstrated no statistically significantly increased risk associated with increased pre-treatment AST, ALT or GGT compared with those with normal pre-treatment liver enzyme levels [1 study; 71 participants; very low quality evidence][373†]

* In these two studies there were fewer than 10 participants with pre-existing liver disease.

† In this study the total number of participants with pre-existing liver disease was unclear.

11.2.16 Risk Factor 6: Cumulative dose of methotrexate

11.2.621 Summary of included studies and results

3 **Table 164: Included studies assessing cumulative methotrexate dose as a risk factor for hepatotoxicity**

Study	N	FU	Gender (M/F%)	Age (years)	Treatment regimen	Treatment (cumulative dose)	Results
Cumulative MTX dose							
Almeyda et al (1972)[384] Retrospective cohort study	67 (42 treated with MTX)	Treatment duration: 3-80 months	58/42 for total sample	Mean 55 (range: 21-77) for total sample	3 dosing schedules 1. 2.5 mg orally 4 or 5 days a week (or daily on alternate weeks; n=11) 2. 12.5-25 mg orally once a week (n=18) 3. 20-40 mg intramuscular or intravenous at weekly or greater intervals (n=38)	Among those treated: **Mean** Normal histology: 0.96g Non-Specific changes only: 1.06g Fibrosis: 1.54g Cirrhosis: 2.73g	**Cumulative methotrexate dose is a risk factor for fibrosis and cirrhosis** • The mean cumulative dose of methotrexate was significantly higher in those with fibrosis and cirrhosis vs those with normal liver biopsy (p=0.05) • The patient with the highest cumulative dose of 5.35g had a normal biopsy, although most of those with a normal biopsy had received less than 1.0g.
Amital et al 2009[385] Retrospective cohort study	809 (n=690 psoriasis, n=119 RA)	Mean follow-up: 883 days (psoriasis group) and 843 days (RA group).	Psor: 48.3/51.7 RA: 34.5/65.5	Psor: mean=52.6 RA: mean=59.9	Unclear	Psoriasis group: 1000 mg RA group: 3625 mg	**Cumulative dose of MTX may be a risk factor for elevated liver enzymes** • Combined results for GGT/ALKP/AST: HR 1.07, 95%CI 1.01 – 1.12, p=0.01 • AST: HR 1.07, 95% CI 1.02 – 1.12, p<0.001 However there was no relationship for the following liver enzymes: • ALKP: HR 1.01, 95% CI 0.95 – 1.08, p=0.69 • GGT: HR 0.86, 95% CI 0.70 – 1.04, p<0.12 • Albumin: HR 0.97, 95% CI 0.70 – 1.34, p=0.85

<table>
<tr><th>Study</th><th>N</th><th>FU</th><th>Gender (M/F%)</th><th>Age (years)</th><th>Treatment regimen</th><th>Treatment (cumulative dose)</th><th>Results</th></tr>
<tr><td>Ashton et al (1982) [368]
Retrospective case series</td><td>56 (38 had pre and post biopsies included in analysis)</td><td>Mean treatment duration: 32.7 months (range: 12-102 months)</td><td>45/55</td><td>Mean: 53 (range: 29-81)</td><td>Oral or intramuscular, up to 30 mg weekly, fortnightly or every 10 days</td><td>Patients with fibrosis: 1955mg over 28mths (average)
Patients without fibrosis: 1920mg over 34mths (average).</td><td>Cumulative methotrexate dose is not a risk factor for hepatotoxicity
No link was demonstrated between the total cumulative dose of methotrexate and hepatotoxicity (although those with fibrosis appeared to have a slightly higher mean dose per month).
<table><tr><th>Group</th><th>N</th><th>Mean MTX dose (mg)</th><th></th></tr><tr><td></td><td></td><td>Total</td><td>Per month</td></tr><tr><td>Total</td><td>38</td><td>1928</td><td>59.0</td></tr><tr><td>Fibrosis</td><td>9</td><td>1955</td><td>69.3</td></tr><tr><td>No fibrosis</td><td>29</td><td>1920</td><td>56.5</td></tr></table></td></tr>
<tr><td>Berends et al (2006) [359]
Retrospective chart review</td><td>125</td><td>Median treatment duration: 228 weeks (range: 16-1763)</td><td>54/46</td><td>Mean: 45.0</td><td>Dosage schedule not stated</td><td>Median: 2113 mg (range: 180-20,235)
(for total group)</td><td>Cumulative methotrexate dose may be a risk factor for biopsy grade progression to Roenigk >1 (not fibrosis)
• Histological progression to a Roenigk grade 2 or higher was most likely when the methotrexate cumulative dose was between 1500mg-6000mg, with limited progression rate below 1500mg
• Progression to higher Roenigk score levelled out above 6000mg, and higher exposure was not associated with any further increase in liver damage.</td></tr>
<tr><td>Boffa et al (1995) [369]
Prospective</td><td>49</td><td>Mean time between first and last</td><td>61/39</td><td>Mean (at last biopsy): 54.8</td><td>Long-term, low-dose once weekly oral MTX (mean weekly dose 10.5 mg;</td><td>Mean at first biopsy: 2743 mg (range: 315-</td><td>Cumulative methotrexate dose is not a risk factor for hepatotoxicity
• There was no significant correlation</td></tr>
</table>

Study	N	FU	Gender (M/F%)	Age (years)	Treatment regimen	Treatment (cumulative dose)	Results
case series		biopsies: 225 weeks (range: 60-460 weeks) Mean duration of treatment 275 (26-738) weeks			range 3.9-19.2 mg)	10,024 mg) plus an average of 2362 mg (range 390-7155mg) during follow-up	between histological group and the dose of methotrexate (cumulative at the time of the last biopsy or dose between biopsies; p=0.23 and p=0.06 respectively). • At the last biopsy, cumulative dose and duration of treatment were also not correlated with the liver histology groups (p=0.46 and p=0.40 respectively).
Khan et al 2006[382] Retrospective case series	65	Mean duration of therapy: 4.3 years	Unclear	Unclear	Not stated	Mean: 2000 mg (SD 1838 mg).	**Cumulative methotrexate dose is a risk factor for hepatotoxicity measured by PIIINP** • Patients with high mean PIIINP levels (>4.2 µg/l) had received significantly higher cumulative dose (>1.5 g) MTX (p=0.002) • The cumulative dose of MTX had significant correlation with the maximum PIIINP levels (p=0.03) • 28% of high PIIINP estimations (>4.2 µg/l) correlated at some stage with an abnormal liver biopsy • Those with fibrosis or cirrhosis (n=4) had received a higher cumulative dose of MTX (median = 4260 mg; mean = 4247.5 mg) than those without fibrosis or cirrhosis (median = 3585 mg; mean = 3811.3 mg).
Lindsay et al (2009) [375] Prospective case series	54	Mean duration of treatment: 6.59 years	N/A	Mean 54.4	Schedule not stated, but 14 on subcutaneous MTX	Mean: 4396 mg (range: 1020-19,657 mg) No Fibrosis:	**Cumulative methotrexate dose is not a risk factor for fibrosis** There is no significant difference in the cumulative dose of methotrexate among

Study	N	FU	Gender (M/F%)	Age (years)	Treatment regimen	Treatment (cumulative dose)	Results
						3839mg (range 1020-19657mg) Fibrosis: 3541mg (range1000-5908mg)	those who developed fibrosis and those who did not: • Median total dose 3839 (1020–19657)mg in those without fibrosis vs 3541 (1000–5908) mg in those with fibrosis
Newman et al (1989)[371] Case series (prognosis)	168 (86 MTX treated)	N/A sample taken from 1968-1986 medical/ office records	52/48 (for total group)	Mean: 47.7 (for total group)	Most received oral administration in either a single weekly or a divided weekly dose MTX treatment stopped when biopsy specimen was grade IIIB or greater	Median monthly MTX dose before biopsy among 86 patients with MTX treatment before biopsy 67.3 (7.5-205.6) mg	**Cumulative methotrexate dose is a risk factor for fibrosis/cirrhosis** • The probability of a normal liver biopsy (grade I or II) decreased with increasing cumulative dose • The probability of a normal liver biopsy result dropped to below 50% when the cumulative dose of methotrexate was 3115 mg (for those who had a pre and post methotrexate biopsy).
Nyfors et al (1976) [379] Case series	88	Average duration of treatment 26 months (range 2-72months)	47.7/52.3	Mean 50 (range: 21-78)	Single, weekly, oral dose of 25 mg maximum	Mean 1733 mg (range: 175-4590 mg)	**Cumulative methotrexate dose is not a risk factor for hepatotoxicity** • No significant correlation between the cumulative methotrexate dose and the number of pathological post methotrexate liver biopsies. • No significant difference in mean cumulative does between the 11 who developed fibrosis or cirrhosis and those whose liver histology remained normal (p = 0.19)
Nyfors et al (1977)[370] Case series	160	Study A – mean treatment duration: 52 months (range: 2-105	Study A-50/50 Study B-49/51	Mean: 57 for both studies	Single weekly oral 25-mg dose maximum	Study A: Mean 2287mg (range: 50-5075 mg) Study B: Mean 3940mg (range 325-8355mg).	**Cumulative methotrexate dose is not a risk factor for fibrosis or cirrhosis** Study A: No significant difference in the cumulative methotrexate dose of those with a normal or cirrhotic/fibrotic liver biopsy, p<0.45.

Study	N	FU	Gender (M/F%)	Age (years)	Treatment regimen	Treatment (cumulative dose)	Results
		months) Study B – Mean time interval between the biopsies is 19months.					Study B: No significant difference in the cumulative methotrexate dose of those with a normal or cirrhotic liver biopsy (3000 mg vs 3061mg, respectively), p=0.245.
Reese et al (1974) [383] Prospective cohort study	70 (50% treated)	Duration of treatment: 0.5-8 years. Second sample taken 6-27 months after the baseline, average 12.4mths	N/A	Mean: 43.4 for MTX treated group; 42.9 for MTX untreated group	Post-biopsy dosing: single intermittent (IM or oral) but moderately high doses (25-50 mg); some cases used the divided dose, intermittent oral schedule over a 36-h period	100-5000 mg (for total group)	**Cumulative methotrexate dose is not a risk factor for hepatotoxicity** • Multivariate analysis demonstrates no effect of methotrexate treatment (compared to untreated patients) on liver biopsies, p=0.4. • Among the 35 treated with methotrexate, the 20 who had some level of fibrosis had a mean MTX dose of 2084.4 mg compared with 2060.9 mg in those without any fibrosis
Roenigk et al (1971) [378] Retrospective cohort study	50 (37 treated)	N/A	56.8/43.2	Post-MTX group: mean 45	Dosing usually 25 mg/week orally	Range: 25-10,000 mg	**Cumulative methotrexate dose is not a risk factor for hepatotoxicity** • No close correlation between the cumulative methotrexate dose and the severity of liver damage. • Mean cumulative dose at time of biopsies showing fibrosis or cirrhosis (n= 8): 2056 mg vs 2037 mg at time of biopsies graded as no fibrosis (n=33)
Tobias et al (1973) [377] Case series	88 (69 treated)	Duration of treatment: 0.1-10 years	44/56	Mean 48.3 (for total group)	Various dosing schedules (no further details given)	Range: 15-9600 mg	**Cumulative methotrexate dose may be a risk factor for portal inflammation, fibrosis and cirrhosis** • Portal inflammation was associated with MTX dose

<table>
<tr><th>Study</th><th>N</th><th>FU</th><th>Gender (M/F%)</th><th>Age (years)</th><th>Treatment regimen</th><th>Treatment (cumulative dose)</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>• Mean cumulative dose increased with increasing biopsy grade
<table><tr><th>Biopsy grade</th><th>N</th><th>Mean cumulative dose (mg)</th></tr><tr><td>Cirrhosis</td><td>5</td><td>4140</td></tr><tr><td>Marked fibrosis</td><td>3</td><td>2933</td></tr><tr><td>Moderate fibrosis</td><td>10</td><td>2760</td></tr><tr><td>Slight fibrosis</td><td>9</td><td>2864</td></tr><tr><td>No fibrosis</td><td>42</td><td>1479</td></tr></table></td></tr>
<tr><td>van Dooren-Greebe et al 1994[381]
Retrospective case series</td><td>113 (48 had biopsy and cumulative dose recorded)</td><td>Mean duration of therapy: 8 years, 11 months</td><td>58.4/41.6</td><td>Mean: 45.5</td><td>Oral MTX: Tx started 3 x 5 mg/week or 3 x 2.5 mg/week (from 1986 onwards), and thereafter gradual dose adjustments were made until a satisfactory minimum maintenance level was reached. Maximum dosage was 15 mg/week.</td><td>Mean cumulative dose: 4803 mg (range 90 mg to 16580 mg).
Weekly dosage did not exceed 15 mg in any patient.</td><td>Cumulative methotrexate dose may be a risk factor for fibrosis/cirrhosis
• In the high dose group (>1.5g): 32/40 (80%) had grades I-II and 8/40 (20%) had grades IIIA-IV
• In the low dose group (≤1.5g): 7/8 (87.5%) had grades I-II and 1/8 (12.5%) had grades IIIA-IV
<table><tr><th rowspan="2">Cumulative dose (mg)</th><th colspan="2">Biopsy grade</th></tr><tr><th>I-II N=39</th><th>IIIA-IV N=9</th></tr><tr><td>0-2000</td><td>8 (20.5%)</td><td>1 (11.1%)</td></tr><tr><td>2001-4000</td><td>9 (23.1%)</td><td>4 (44.4%)</td></tr></table></td></tr>
</table>

Study	N	FU	Gender (M/F%)	Age (years)	Treatment regimen	Treatment (cumulative dose)	Results		
							4001-6000	9 (23.1%)	2 (22.2%)
							6001-8000	6 (15.4%)	1 (11.1%)
							8001-10000	7 (17.9%)	0
							10001-12000	0	1 (11.1%)
No authors listed (1973)[374] Case series and within-group analysis	550	Mean treatment duration: 2.8±2.0 years	57/43	Mean: 46.9	1. Daily oral administration of low doses interspersed with rest periods 2. Weekly oral administration of a single dose 3. Weekly intra-oral or intramuscular administration of a single dose 4. Weekly oral administration of divided dosage; 3-4 dosages over a 36-h periods weekly	1.84 g	**Cumulative methotrexate dose is a risk factor for cirrhosis, fibrosis and inflammation** • Increasing cumulative dose of MTX correlated significantly with periportal inflammation (p<0.001), fibrosis (p<0.001) and cirrhosis (p<0.002)		
Wollina et al 2001[380] Retrospective case series	104	N/A	58/42	Mean: 27.7	MTX was given once a week in an individualised dosage (7.5 to 40 mg iv or oral) followed by 15 mg folate orally the next day	≤2000 mg (N=23) >2000 mg (N=81)	**Cumulative methotrexate dose may be a risk factor for fatty change and for elevated liver enzymes** • Serum enzyme increase >2.5 x ULN: 35% in low dose group vs 52% in high dose group • Fatty change: 15% in low dose group vs 32% in high dose group		

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11.2.612 Evidence statements: Cumulative MTX dose

There was inconsistency between studies assessing the risk of hepatotoxicity associated with cumulative methotrexate dose in people with psoriasis. This was true for the majority of outcomes as outlined below:

- Composite outcome of fibrosis and/or cirrhosis
  - 2 studies demonstrated a statistically significantly increased risk associated with cumulative methotrexate dose [592 participants; very low quality evidence] [374,384]
  - 3 studies suggested an apparent increased risk associated with cumulative methotrexate dose [285 participants; very low quality evidence][359,371,377,381]
  - 2 studies demonstrated no statistically significantly increased risk associated with cumulative methotrexate dose [248 participants; very low quality evidence] [370,379]
  - 1 study suggested no apparent increased risk associated with cumulative methotrexate dose [41 participants; very low quality evidence] [378]
- Fibrosis
  - 1 study demonstrated no statistically significantly increased risk associated with cumulative methotrexate dose [54 participants; very low quality evidence] [375]
  - 2 studies suggested no apparent increased risk associated with cumulative methotrexate dose [73 participants; low to very low quality evidence] [368,383]
- Fatty change
  - 1 study suggested an apparent increased risk associated with cumulative methotrexate dose [104 participants; very low quality evidence][380]
- Liver inflammation
  - 1 study demonstrated a statistically significantly increased risk associated with cumulative methotrexate dose for periportal inflammation [1 study; 550 participants; very low quality evidence] [374]
  - 1 study suggested an apparent increased risk associated with cumulative methotrexate dose for increased portal inflammation [1 study; 69 participants; very low quality evidence] [377]
- Non-invasive liver tests
  - 2 studies demonstrated a statistically significantly increased risk associated with cumulative methotrexate dose; one used the outcome of high PIIINP [1 study; 65 participants; very low quality evidence][382] while another used increased liver enzymes (combined results for GGT/ALKP/AST; or AST alone) [1 study; 809 participants; low to very low quality evidence][385]
  - 1 study suggested an apparent increased risk associated with cumulative methotrexate dose for serum enzyme increase [104 participants; very low quality evidence][380]
  - 1 study demonstrated no statistically significantly increased risk associated with cumulative methotrexate dose for the outcome of increased liver enzymes (GGT, ALKP or albumin alone) [809 participants; low to very low quality evidence][385]
- Biopsy grade
  - 1 study suggested an apparent increased risk associated with cumulative methotrexate dose for progression to a Roenigk grade 2 or higher (up to 6000 mg MTX)[1 study; 125 participants; very low quality evidence] [359]
  - 2 studies demonstrated no statistically significantly increased risk associated with cumulative methotrexate dose; one used the outcome of severity of hepatotoxicity [1 study; 49 participants; low quality evidence] [369], while the other reported change in histology [1 study; 49 participants; low quality evidence] [369]

- 1 study suggested no apparent increased risk associated with cumulative methotrexate dose [37 participants; very low quality evidence] [378]

- Abnormal liver histology
  - 1 study demonstrated no statistically significantly increased risk associated with cumulative methotrexate dose [35 participants; low quality evidence] [383]

11.3 Children

11.3.1 Risk Factor 1: Obesity

No studies in children were found that looked at the other risk factors.

11.3.1.1 Summary of included studies and results

Table 165: Included studies assessing obesity as a risk factor for hepatotoxicity in children

Study	N	N with risk factor	Follow up	Gender (M/F%)	Age (years)	Treatment (cumulative dose)	Results
Pre-existing liver disease							
Collin et al (2009) [24] Retrospective case series (prognosis)	13	3	Mean treatment duration: 71 weeks	31/69	Mean: 12.1	Range: 45-3637.5 mg	**Obesity may increase the risk of hepatotoxicity (disturbed liver function tests) in children** • 3/13 cases were obese and 2 of these 3 had disturbed liver function tests vs 0 of the 10 non-obese children

11.3.1.2 Evidence statement

One study showed an apparent link between obesity and hepatotoxicity. The outcome was:

- Disturbed liver function tests in children [1 study; 13 participants; very low quality evidence] [24*]

*This study had only 3 participants with obesity.

11.3.12 Economic evidence

2 No relevant economic evidence was identified.

11.4 Recommendations and link to evidence

Recommendations	**No recommendatrions made**
Future research recommendations	**22. What is the impact of methotrexate compared with other approaches to care (for example, other systemic non-biological or biological therapies) on risk of significant liver disease in people with psoriasis and do risk factors such as obesity, alcohol or diabetes alter this risk?**
Relative values of different outcomes	The outcomes considered were: • liver fibrosis • cirrhosis of the liver • hepatotoxicity (abnormal liver function tests) • biopsy grade • biopsy grade progression • fatty change • periportal inflammation The group members agreed to focus on cirrhosis and fibrosis as these are the key clinical outcomes. Evidence for short term liver toxicity (as indicated by rise in transaminases) has been reviewed in chapter 9.
Trade off between clinical benefits and harms	Methotrexate is a useful drug for long term disease management. The absolute risk of clinically significant liver fibrosis or cirrhosis due to methotrexate per se is unknown and maybe lower than is perceived by patients and some clinicians. In clinical practice, methotrexate may not be prescribed in the presence of risk factors for liver fibrosis (for example, hepatic steatosis in relation to obesity, diabetes) although the evidence does not support this. Complete avoidance or minimal intake of alcohol is standard advice for patients taking methotrexate and is a barrier to some people who would benefit from using methotrexate. The evidence did not support this and with appropriate patient selection and strict monitoring, alcohol may be allowable.
Economic considerations	No evidence was available to inform the GDG about the economic impact of methotrexate associated hepatotoxicity, nor on how lower or higher risks would impact its cost-effectiveness as a treatment for people with psoriasis. Economic evaluations assessing the cost-effectiveness of methotrexate compared to other systemic biological and non-biological treatments have not captured risks of hepatotoxicity due to inconclusiveness of the clinical evidence and the complexity it would add to any decision model. These same evaluations have found methotrexate to be cost-saving compared to or more cost-effective than alternatives,

	including no treatment, ciclosporin and various biological therapies. Its dominance over most other therapies is largely driven by its extraordinarily low acquisition cost compared to other drugs. The GDG concluded that despite the potentially higher risks of liver toxicity, methotrexate is still likely to be an optimal treatment and that the additional costs of extra monitoring were unlikely to alter this conclusion.
Quality of evidence	Many of the studies are old and are based on small sample sizes. The studies did not clearly state whether confounding variables had been assessed, including whether liver pathology was present prior to MTX administration; therefore consideration was given to whether the GDG could be confident the effect is due to the risk factor. There are limitations with assessing liver damage using liver biopsy due to variation in sampling technique (which was poorly reported) and patch pathological change .There is also variation in the histology grading scales used in the different studies, and it was not possible to map them to a common scale. Some studies had performed statistical analyses (in most cases by looking at the degree of correlation between the risk factor and the outcome), while others had not (in which case results are reported as an apparent or no apparent effect). The GDG noted that an apparent effect could have been non-significant. Studies used different definitions of alcohol consumption and some definitions are vague. Also, the intake is often based on self-reporting which may be inaccurate. However, there was no consistent pattern to suggest that studies using a stricter definition of high alcohol intake were the ones that demonstrated a link. In light of these issues, the group interpreted the evidence with caution. **For alcohol as a prognostic factor:** Most of the data related to alcohol intake before MTX use, but intake during MTX use may be more important. Data for intake both before and during methotrexate use were given in 2 studies(Nyfors 1977 and Boffa). These data suggested that the intake during therapy may be more of a risk for liver damage (e.g., those with the greatest decrease in alcohol intake showed the lowest liver histology score [Boffa] and there was a significant link between liver damage and alcohol intake during therapy but only a modest apparent link with alcohol intake prior to therapy [Nyfors 1977]) **For cumulative MTX dose as a prognostic factor:** The Berends study showed that biopsy grade progression levelled out above 6000mg but this was defined as progression to grade>1 (not fibrosis) and people could still have been progressing to

higher severity within the category of grade >1.

The Newman study reported that the probability of normal biopsy (Grade I or II) dropped below 50% at 3115 mg.

The heterogeneous results were not explained by treatment duration, age, treatment regimen or mean cumulative dose (i.e., there was no consistent pattern, for example, those that showed a link used oral MTX or had a higher mean cumulative dose). The variable results could be due to individual differences in tolerance of high MTX dose (demographics not controlled for).

The GDG noted that all 3 of the prospective and both studies that adjusted for confounders showed no significant link.

From the studies, there was no consistent and methodologically robust evidence to conclude that for people with psoriasis taking methotrexate there are any groups who are at higher risk of methotrexate-induced liver damage. The risk of liver damage is already raised among people with psoriasis. Large, well-designed studies would need to be performed in order to correct for all confounders. At present there may be a reluctance in clinical practice to use methotrexate in people with psoriasis who have risk factors and/or reluctance to continue methotrexate with high cumulative doses (>3g). The evidence does not support this.

Overall, the evidence for risk factors is poor, and there are a number of important confounders in the studies that make it difficult to evaluate the role of methotrexate itself. There is no consistent evidence that any of the risk factors, including cumulative dose of methotrexate, increase the risk of liver fibrosis or cirrhosis. Therefore the GDG did not wish to make a recommendation about at risk groups.

From the evidence, there are no groups in whom we would not recommend methotrexate. There is no consistent evidence that any specific group is at an increased risk. Therefore risk factors cannot be used as a screening tool. All patients should be evaluated prior to and after commencing treatment.

The GDG agreed there was no consistent and methodologically robust evidence to conclude that that for people with psoriasis taking MTX there are any groups who are at particularly high risk of methotrexate-induced hepatotoxicity, including cumulative dose of methotrexate. However, all people with psoriasis may be at increased risk of liver disease so large, well-designed studies would need to be performed in order to properly correct for all the confounders.

At present there may be a reluctance in clinical practice to use methotrexate in people with psoriasis who have risk factors and/or reluctance to continue methotrexate with high cumulative doses (>3g). However, there is not robust evidence to underpin this tendency.

	Recommendations about monitoring for hepatotoxicity can be found in chapter 11.
Other considerations	The group considered referencing the government guidance on recommended daily alcohol intake. It was felt that this may not be appropriate, as the recommended daily amounts of alcohol are applicable to the general population, not people with psoriasis. Evidence from chapter 6.4 indicating an increased risk of alcohol-related death would support this contention. The group felt there was a need to act responsibly when formulating the recommendations. The evidence did not show any consistent signal that alcohol intake increased the risk of liver damage on methotrexate, but there were methodological limitations which meant that the GDG had little confidence in the results. As such the GDG were unable to make a recommendation either way (i.e. that alcohol should be completely avoided, or that alcohol was permissible during therapy). Methotrexate induced liver problems are an important concern to both clinicians and patients and a common cause for patients to decline therapy and/ or clinicians to stop/not offer this therapy. Well conducted research is required to establish the risk of liver disease in people with psoriasis per se, whether methotrexate adds to the risk, and the contribution of factors such as alcohol, obesity or diabetes to any identified risk. Research in this area would need to involve large numbers of patients given that the absolute risk of liver fibrosis may be low, control properly for confounders (obesity, diabetes, alcohol), and use validated outcomes that overcame the identified difficulties in the existing studies (different reporting scales, lack of clinically relevant outcomes).

12 Methotrexate and monitoring for hepatotoxicity

The risk of liver fibrosis is an accepted but unknown risk associated with methotrexate. Histological evaluation of a liver biopsy specimen is currently the gold standard for diagnosing, staging and monitoring liver fibrosis due to any cause but the procedure of liver biopsy carries significant morbidity and mortality, and is disliked by patients. The need for liver biopsy is commonly cited as a reason for dissatisfaction with treatment by patients, or for discontinuing therapy when biopsy is felt to be necessary[387]. In addition, the technique is subject to sample errors, since the samples collected are very small and pathological change may not be evenly distributed, and interpretation varies amongst histologists depending on level of experience, size of biopsy and use of staging / scoring system . Given the limitations of liver biopsy, significant effort has been invested in identifying clinical useful, non invasive markers of liver fibrosis that allow identification and quantification of liver fibrosis[388]. Fibroelastography (achieved using the FibroScan®) gives a measure of liver of elasticity (and therefore fibrosis) by measuring reflected ultrasound echoes before and during compression of the liver. The degree of displacement is related to the tissue elasticity stiffness. This method has been used to evaluate and track fibrosis in chronic liver disease[389], and, as indicated in recent systematic review and economic analysis by the NHS Centre for Evidence-based purchasing[390], may have clinical utility for the detection and monitoring of fibrosis due to other causes. Serum biomarkers of liver fibrosis focus on indirect markers of liver function or direct markers of extracellular matrix components or the enzymes involved in their turnover. Indirect markers of liver function include aspartate aminotransferase (AST), alanine aminotransferase (ALT), c-glutamyl transpeptidase(c-GT), hyaluronic acid, apolipoprotein A1, bilirubin, a2-macroglobulin, haptoglobin, cholesterol, homeostasis model assessment of insulin resistance, platelets and prothrombin time. Direct markers of liver function include collagen IV, collagen VI, tissue inhibitor of metalloproteases-1 (TIMP-1), laminin, human cartilage glycoprotein-39 (YKL-40), tenascin, undulin, matrix metalloproteinase-2 (MMP-2) and pro-collagen III propeptide (PIIINP)[391]. Some of these biomarkers have been combined to improve clinical utility (for example, the European Enhanced Liver Fibrosis ELF panel which combines hyaluronic acid, TIMP-1 and PIIINP measurements).

For the last 5 - 10 years, serial measurement of PIIINP has become standard practice[392] for monitoring for liver fibrosis in patients on methotrexate, with elevated levels indicating the need for treatment cessation and/or consideration of liver biopsy. Given the high level of concern amongst clinicians and patients about methotrexate-associated liver dysfunction and the plethora of new indirect markers of liver disease, the GDG agreed it important to review the evidence for the clinical utility and validity of these markers of liver fibrosis in the context of psoriasis and treatment with methotrexate in order to optimise the safe use of this drug, and minimise the need for liver biopsy.

The GDG agreed to pose the following question: in people with psoriasis (all types) who are being treated with methotrexate or who are about to being treatment with methotrexate, what is the optimum method and frequency of monitoring hepatotoxicity (hepatotoxicity or cirrhosis)?

12.1.1 Methodological introduction

12.1.1.1 Review methods

A literature search was conducted for diagnostic cohorts or case control studies that assessed the accuracy of non-invasive diagnostic tools to detect liver fibrosis or cirrhosis in people with psoriasis being treated or considered for treatment with methotrexate, compared with diagnosis by the reference standard of liver biopsy.

No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The relevant population for these diagnostic tools will be those with psoriasis who are at risk of developing liver damage as a result of exposure or planned exposure to methotrexate. The intended role of the index test would be for use by dermatologists to identify those suspected of having clinically significant liver damage in order to refer only these people on for expert assessment and, therefore, reduce the need for the invasive procedure of liver biopsy. Consequently, it is most important that the test is able to accurately rule-out a diagnosis, so that very few people with liver damage are missed for referral, although a reasonable accuracy for ruling-in a diagnosis would also be desirable to avoid referring too many people inappropriately.

The outcomes considered were:

- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Likelihood ratios (LRs)

The comparisons considered were any of the following diagnostic tests compared with liver biopsy:

- imaging techniques: liver ultrasound, liver scintigraphy, ultrasound elastography (achieved using the FibroScan)
- serum markers: serial pro-collagen III (PIIINP), the enhanced liver fibrosis (ELF) panel (tissue inhibitor of matrix metalloproteinase 1 (TIMP 1), hyaluronic acid (HA) and pro-collagen III), and FibroTest
- AST to platelet ratio index (APRI)
- Standard liver function tests (e.g., alanine aminotransferase (ALT), alkaline phosphatase (AP), aspartate aminotransferase (AST), total bilirubin, albumin, total protein, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT) and prothrombin time (PT))

It was recognised that there was great variability in the literature regarding definitions of abnormal results on both liver biopsy and non-invasive tests. For the liver biopsy findings, any definition of fibrosis or cirrhosis, regardless of the classification scale, was accepted as indicating clinically significant liver damage. However, studies that limited the definition to at least marked fibrosis were excluded as they may overestimate the sensitivity by removing the potentially more difficult to diagnose milder end of the fibrosis spectrum. Additionally, fibrosis and cirrhosis were considered together as there were few cases of cirrhosis reported and many studies did not give the number with fibrosis and cirrhosis separately, although it is accepted that cirrhosis represents a greater clinical burden. The experience of the pathologist assessing the biopsy sample and the adequacy of sampling of the histological specimen are probably more important in terms of accurate diagnosis than the classification system used, but these were rarely stated in the studies. For the non-invasive tests, the definition of abnormal liver function provided in the study was accepted for use in the analysis, because, for example, there are no universally accepted reference ranges for liver function tests and the ranges may differ according to the population being studied (anything above the upper limit of normal was accepted as an abnormal reading in this review).

It was not possible to analyse the data using diagnostic meta-analysis (because there were no cases with at least 5 studies addressing the same reference standard and index tests, population and outcomes) or the standard version of GRADE. Therefore, a modified version of GRADE has been used and a narrative summary provided. The statistics used for this diagnostic review differ from those used in intervention reviews, and a definition for each of them is provided below (Table 166). Although no meta-analysis has been performed, forest plots are provided presenting the sensitivity and specificity of the tools compared with biopsy findings as reported in the studies individually (Appendix J). There are no forest plots for one study[371], as insufficient raw data were available.

Table 166: Definitions of summary statistics for diagnostic accuracy studies

Measure	Definition
True positives (TP)	Correct positive test result - number with fibrosis or cirrhosis with a positive index test result
True negatives (TN)	Correct negative test results - number without fibrosis or cirrhosis with a negative index test result
False positives (FP)	Incorrect positive test result - number without fibrosis or cirrhosis with a positive index test result
False negatives (FN)	Incorrect negative test result - number with fibrosis or cirrhosis with a negative index test result
Sensitivity	Proportion of those with the disease (based on reference standard) who are positive on the index test
Specificity	Proportion of those without the disease (based on reference standard) who are negative on the index test
Positive predicative value (PPV)	Probability of having the disease in a patient with a positive index test result
Negative predicative value (NPV)	Probability of not having the disease in a patient with a negative index test result
Positive likelihood ratio (LR+)	The number of times more likely a positive test result is in a person with compared to a person without the disease (therefore LR+ is >1)
Negative likelihood ratio (LR-)	The number of times more likely a negative test result is in a person with compared to a person without the disease (therefore LR- is <1)

Positive and negative predicative values are dependent on disease prevalence (pre-test probability) and so need to be interpreted together with prevalence, in the context of how test results modify the probability of disease (post-test probabilities). Consider that the lower the prevalence of disease the more certain we can be that a negative test indicates no disease, and the less certain that a positive result truly indicates the presence of disease. A note on how to interpret post-test probabilities/predictive values in the light of the disease prevalence is provided in Appendix Q.

Fifteen diagnostic studies[298,371,372,392-403] were found that addressed the question and were included in the review. No studies were available that from an exclusively paediatric population.

These studies differed in terms of:

- Mean age (range 46 to 55 years)
- Gender: % male (range 52 to 71.4%)
- Sample size (range N=15 to N=168)
- Prevalence of fibrosis and cirrhosis (6.9-69.5%)
- Unit of analysis
    - 8 studies used only one index test and one reference standard per person[298,392,393,395,397,399,401,402]
    - 3 studies included multiple paired index and reference tests per person[394,396,398]
    - 1 study included only single pre-MTX tests but multiple paired tests post-MTX[372]
    - In 2 studies it was unclear whether the results were based upon single tests or multiple paired tests per person[371,403]
    - 1 study included more than one index and reference test per patient, and also more than one index test per reference standard (i.e. the biopsy was paired with more than one index test)[400]

A summary of the methodological quality of the included studies according to QUADAS II criteria is provided in Table 167.

1 **Table 167: Summary of study quality**

Study	N	Index test(s)	Selection criteria	Reporting bias	Verification bias[a]	Time between tests[b]	Index test threshold selection	Blinding of assessors	Experienced assessor	Adequate biopsy sample
Liver function tests										
Ho 1986 (prospective)	18	**LFT:** ALT	Consecutive sample, all receiving MTX (Singapore)	Yes	Yes – only included those with high ALT or high total MTX dose	Unclear	Unclear	Yes	Unclear	Unclear
Lenler-Peterson 1982 (retrospective)	45 (151 concurrent tests)	**LFT:** galactose tolerance test	Consecutive sample, all receiving MTX and having developed fibrosis	Yes	Yes – only included those known to have developed fibrosis	Unclear[c]	Pre-defined	Unclear	Unclear	Unclear
Newman 1989 (retrospective)	168 (364 biopsies paired with LFTs, 85 before treatment)	**LFTs:** ALT, AST, bili, AP, PT, alb	Consecutive sample, before and during MTX	Unclear if all analysed	No	3 days	Unclear	Yes	Unclear (but IRR of 3 assessors checked)	Unclear
O'Connor 1989 (retrospective)	78 (147 biopsies paired with LFTs; 52 before and 95 after treatment)	**LFTs:** AST, bili, AP	Unclear sampling, all had used MTX (normal pre-Tx biopsy)	No	No	Maximum 1 week	Pre-defined normal ranges	Yes	Unclear	Unclear
Paramsothy 1988 (prospective)	15	**LFTs:** AST, bili, AP, alb, GGT	Unclear sampling, all had used MTX	Yes	No	Unclear	Pre-defined normal ranges	Yes	Unclear	Unclear
Liver scintigraphy and ultrasound scans										
Geronemus 1982 (retrospective)	24	**Liver scintigraphy:** Tc 99m sulphur colloid scan	Unclear sampling, all had long-term MTX use	Yes	No	Maximum 2 months	Pre-specified	Unclear	Unclear	Unclear
McHenry 1992 (retrospective)	63 (87 paired results)	**Liver scintigraphy:** Tc 99m sulphur	Consecutive sample, before and during MTX	No	No	Maximum 4 weeks	Pre-specified	Unclear	Unclear	Unclear

Study	N	Index test(s)	Selection criteria	Reporting bias	Verification bias[a]	Time between tests[b]	Index test threshold selection	Blinding of assessors	Experienced assessor	Adequate biopsy sample
		colloid scan								
Mitchell 1987 (prospective)	49	**Liver scintigraphy:** Tc 99m sulphur colloid scan **Ultrasound**	Unclear sampling, all had long-term MTX use	No	No	1 day	Pre-specified	Unclear	Yes	Unclear
Coulson 1987 (prospective)	28 (54 paired tests)	**Ultrasound**	Unclear sampling, before and during MTX	No	No	Maximum 1 month	Pre-specified	Yes	Yes for ultrasound; unclear for biopsy	5 µm sections
PIIINP										
Boffa 1996 (prospective)	87 (147 paired tests)	**PIIINP**	Unclear sampling, all had long-term MTX use Note: unclear proportion with PsA	No	No	<1 day	Pre-specified[d]	Yes	Unclear	Unclear
Maurice 2005 (retrospective)	34 (46 biopsies with 2-6 assays per biopsy)	**PIIINP**	Consecutive sample, all receiving MTX Note: 22% had inflamm. arthritis	No	No	Maximum 6 months	Pre-specified[d]	Yes	Unclear	18 gauge needle
Zachariae 1989 & Risteli 1987 (prospective)	73	**PIIINP**	Consecutive sample, all receiving MTX (≥6 months) Note: 45.8% of pilot group had PsA	Yes	No	Unclear	Pre-specified[d]	Yes	Unclear	Unclear
Zachariae 2001 (retrospective)	70 (189 biopsies and 329 assays)	**PIIINP**	Unclear sampling, all had MTX use and normal initial biopsy and PIIINP Note: 38.6% had PsA	Yes	No	69/70 had ≥3 analyses within a year around the	Pre-specified[d]	Unclear	Unclear	Unclear

Study	N	Index test(s)	Selection criteria	Reporting bias	Verification bias[(a)]	Time between tests[(b)]	Index test threshold selection	Blinding of assessors	Experienced assessor	Adequate biopsy sample
						time of biopsy				
Fibrotest and Fibroscan										
Berends 2007 (retrospective)	24	**Fibrotest** **Fibroscan -** used median value of successful readings on the same day	Unclear sampling	Yes	No	≤18 months	Pre-specified	Yes	Yes	Variable (only one had <10 portal tracts)

Alb: albumin; ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; bili: bilirubin; GGT: gamma-glutamyl transferase; IRR: inter-rater reliability; LFT: liver function tests; MTX: methotrexate; PIIINP: aminoterminal peptide of type III procollagen; PsA: psoriatic arthritis; PT: prothrombin time; Tc 99m: Technetium-99m isotope; Tx: treatment

(a) Verification bias = did all patients in the studies received the same comparison tests, regardless of initial results

(b) Clearly, if the time between the index test and the reference standard is too long it is possible that any discrepancy in findings is not accounted for by inaccuracy in the index test but rather y the clinical status of the participant having changed in the intervening period. However, the time for progression to fibrosis is unclear and any cut-off for a maximum time between tests would be arbitrary; therefore, all studies were included regardless of time between tests, although this will be considered as a risk of bias

(c) Study methods state that participants were admitted at 1-year intervals for biopsy and galactose test, which implies they were performed on the same day

(d))The threshold for an abnormal PIIINP assay was >4.2 µg/l (based on the reference range in Finnish blood donors); however, the manufacturer's information leaflet states that the reference range is 2.3-6.4 µg/l based on PIIINP values of apparently healthy adults (19-65 years) although variations in population demographics may mean that slightly different reference limits apply across populations.

12.112 Study details – methods and results

The study methods are graded in the evidence profile (Table 168) and a summary of the study results is provided inTable 169. In the narrative below, methodological flaws according to the QUADAS II criteria are noted as points to suggest caution when interpreting results.

12.113 Liver function tests

Methods

Five studies were found that investigated the diagnostic accuracy of liver function tests in people with psoriasis eligible to receive methotrexate. The reference standard biopsy classification varied between the studies; two studies[371,372] used the Roenigk classification system, 2 studies used a system similar to Robinson grading[298,393] and in one paper the classification system was unclear[394].

Two of the studies limited the population to those with known[394] or suspected[393] fibrosis. Two of the studies[371,393] had an unclear method for determining the index test threshold, which could have meant that a cut-off was chosen in a post-hoc manner to optimise the apparent sensitivity of the test. Three of the studies[298,393,394] had an unclear period of time between the index test and reference standard.

Results

Sensitivity: of patients with fibrosis or cirrhosis on biopsy, the proportion expected to test positive

- Albumin: 19-29%
- ALT: 5-40%
- AP: 38-57%
- AST: 20-43%
- Bilirubin: 0-20%
- Galactose: 14%
- GGT: 33%
- Prothrombin time: 1%

Specificity: of patients without fibrosis or cirrhosis on biopsy, the proportion expected to test negative

- Albumin: 76-100%
- ALT: 85-92%
- AP: 71-76%
- AST: 86-100%
- Bilirubin: 86-96%
- Galactose: 94%
- GGT: 63%
- Prothrombin time: 99%

Positive predictive value (figure in brackets is value-added PPV; the improvement in ability to determine a positive diagnosis over and above the known prevalence): if the liver function test was positive the probability of having liver fibrosis or cirrhosis (PPV) was:

- AP: 15-60% (5 to 16%)

- ALT: 22-67% (22-39%)
- Albumin: 33-100%
- Bilirubin: 0-41% (-47 to 23%)
- Prothrombin time: 25% (NA)
- AST: 29-100% (19-53%)
- GGT: 40% (-2.9%)
- Galactose: 83% (13.8%)

Negative predictive value: if the liver function test was negative the probability of not having liver fibrosis or cirrhosis (NPV) was:

- Albumin: 61-62% (38-39% chance of having liver fibrosis or cirrhosis despite having a negative test)
- ALT: 52-80% (20-48% chance of having liver fibrosis or cirrhosis despite having a negative test)
- AP: 60-92% (8-40% chance of having liver fibrosis or cirrhosis despite having a negative test)
- AST: 62-93% (7-38% chance of having liver fibrosis or cirrhosis despite having a negative test)
- Bilirubin: 50-91% (9-50% chance of having liver fibrosis or cirrhosis despite having a negative test)
- Galactose: 32% (68% chance of having liver fibrosis or cirrhosis despite having a negative test)
- GGT: 56% (44% chance of having liver fibrosis or cirrhosis despite having a negative test)
- Prothrombin time: 66% (34% chance of having liver fibrosis or cirrhosis despite having a negative test)

Positive likelihood ratio: in a person with compared to a person without liver fibrosis or cirrhosis, the number of times more likely a positive test result is:

- Albumin: infinity
- AP: 1.71-2.03
- ALT: 2.6-5.2
- AST: 3.13-infintiy
- Bilirubin: 1.57-4.7
- Galactose: 2.19
- GGT: 0.89

Negative likelihood ratio: in a person without compared to a person with liver fibrosis or cirrhosis, the number of times more likely a negative test result is:

- Albumin: 1.4
- AP: 1.3-1.7
- ALT: 1.4-1.5
- AST: 1.4-1.5
- Bilirubin: 0.88-1.2
- Galactose: 1.1
- GGT: 0.93

Additional information

- One study[372] assessed subgroups before and during methotrexate treatment and showed no consistent trend among the different liver function tests for differing accuracy before and after treatment was commenced

- One study[372] assessed the statistical association between abnormal liver function tests and biopsy grade III or IV, adjusted for age and history of cholecystitis. This study found that there was a significant association between grade III or IV biopsy findings and abnormal AST, but not ALP or bilirubin, levels
- In one study[393], the one case of cirrhosis was not detected by abnormal liver function tests

12.1.361 Liver scintigraphy

Methods

Three studies[395-397] were found that investigated the diagnostic accuracy of liver scintigraphy in people with psoriasis eligible to receive methotrexate. The reference standard biopsy classification varied between the studies; one study[395] used the Roenigk classification system, one study[396] graded fibrosis as none, very mild, mild, moderate or severe based on the method of Warin et al (abnormal was defined as at least moderate fibrosis, which maps on to the fibrosis assessed on the Roenigk scale) and the final study[397] graded the biopsy according to steatosis, inflammation, fibrosis (graded mild, moderate or severe) and cirrhosis. The definition of abnormal on the liver scan also varied between the studies: one study[395] counted the presence of any one from heterogeneous uptake, hepatomegaly, extra hepatic uptake and focal defects; another[397] assessed the size of the liver and spleen, the pattern of uptake in these organs and the degree of extrahepatic uptake; and the third[396] classified abnormal as a portal contribution of <50% of total hepatic uptake of colloid at 30s. None of the studies specified whether the assessors were blinded to the results of the first test.

Results

Sensitivity and specificity: The findings for the sensitivity and specificity of liver scans varied between the studies. The sensitivity ranged from 50.0 to 83.3% and specificity from 64.7 to 81.5%. Sensitivity and specificity were highest in the study that defined abnormal results on the scan as <50% portal contribution, which also had by far the lowest prevalence of liver fibrosis or cirrhosis and used the definition of at least moderate fibrosis.

Positive predictive value/negative predictive value: If the scan was positive the probability of having liver fibrosis or cirrhosis (PPV or proportion of patients with a positive test who are correctly diagnosed) ranged from 25 to 40% and if the scan was negative the probability of not having liver fibrosis or cirrhosis (NPV or proportion of patients with a negative test who are correctly diagnosed) ranged from 78.6 to 98.5% (1.5 to 21.4% chance of having fibrosis or cirrhosis despite having a negative test).

Given that the pre-test probabilities of having fibrosis/cirrhosis were 29.2, 6.9 and 24.5% in the three populations, this means that the liver scan improves the ability to determine a positive diagnosis (over and above the known prevalence) by 10.8 to 18.8% and a negative diagnosis by 5.3 to 7.8%.

Likelihood ratio: A positive test result ranged from 1.62 to 4.50 times more likely in a person with compared to a person without fibrosis/cirrhosis, and a negative test result ranges from 1.5 to 5.0 times more likely in a person without compared to a person with fibrosis/cirrhosis. Both the positive and negative likelihood ratios were much more favourable in the study that defined abnormal results on the scan as <50% portal contribution, which also had by far the lowest prevalence of liver fibrosis or cirrhosis and used the definition of at least moderate fibrosis[396].

Additional information

One study[396] noted that the one false negative result had a portal contribution of 51% so a slight alteration in the threshold would have resulted in all patients with portal fibrosis to be detected by the scan.

In one study[395], the two cases of cirrhosis were correctly identified.

12.1.362 Liver ultrasound

Methods

Two studies[397,398] were found that investigated the diagnostic accuracy of liver ultrasound in people with psoriasis eligible to receive methotrexate. The reference standard biopsy classification varied between the studies; one study[397] graded the biopsy according to steatosis, inflammation, fibrosis (graded mild, moderate or severe) and cirrhosis and the other study[398] graded the biopsy by subjective microscopic assessment based on the method of Warin et al of fat, inflammation, fibrosis (each graded 0, 0.5, 1, 2, or 3) and cirrhosis (not graded). The definition of abnormal on the ultrasound scan also varied between the studies: one study counted the presence of abnormalities in any one from liver size, shape, echo pattern and information about the biliary and vascular system according to a standard proforma while the other assessed fatty change and fibrosis (only those showing fibrosis were counted as positive tests).

One study[397] did not specify whether the assessors were blinded to the results of the first test.

Results

Sensitivity and specificity: The findings for the sensitivity and specificity of ultrasound scans varied between the studies. The sensitivity ranged from 0 to 19% and specificity from 86 to 100% for detecting any degree of fibrosis and were 25% and 100%, respectively, for detecting portal fibrosis (in accordance with Roenigk criteria).

Positive predictive value/negative predictive value: If the ultrasound scan was positive the probability of having liver fibrosis or cirrhosis (PPV or proportion of patients with a positive test who are correctly diagnosed) ranged from 0 to 100% and if the scan was negative the probability of not having liver fibrosis or cirrhosis (NPV or proportion of patients with a negative test who are correctly diagnosed) ranged from 57 to 73% (27 to 43% chance of having fibrosis or cirrhosis despite having a negative test).

Given that the pre-test probabilities of having fibrosis/cirrhosis were 24.5, 48.2 and 37.0% in the three populations, this means that the liver scan improves the ability to determine a positive diagnosis (over and above the known prevalence) by -24.5 to 63.0% and a negative diagnosis by -2.5 to 6.0%.

Likelihood ratio: A positive test was infinitely more likely in a person with compared to a person without fibrosis/cirrhosis in two studies but equally likely in another study, and a negative test result ranged from 0.86 to 1.2 times more likely in a person without compared to a person with fibrosis/cirrhosis.

The difference in accuracy for detecting any compared with portal fibrosis was less pronounced than with scintigraphy

Additional information

- In one study[397] ultrasound failed to detect any of the three cases of fibrosis or cirrhosis.

12.1.313 PIIINP

Methods

Four studies[392,399-402] were found that investigated the diagnostic accuracy of PIIINP assays in people with psoriasis eligible to receive methotrexate. The reference standard biopsy classification varied between the studies; one study[400] used the Roenigk classification system, one study[392] graded the biopsy according to steatosis, inflammation, fibrosis and cirrhosis and the other two studies did not define the classification systems used[399,402]. All studies conducted more than one assessment of PIIINP per person and the threshold for an abnormal PIIINP assay was >4.2 µg/l (based on the reference range in Finnish blood donors); however, the manufacturer's information leaflet states that the reference range is 2.3-6.4 µg/l based on PIIINP values of apparently healthy adults (19-65 years), although variations in population demographics may mean that slightly different reference limits apply across populations.

Although all studies performed more than one PIIINP assay per person, for the analysis of diagnostic accuracy not all of the test results were always included:

- One study[392] serially assessed PIIINP and used only the PIIINP assay taken at the time of first biopsy
- One study[401,402] had serial PIIINP assays in 11 out of 74 participants and used the PIIINP assay taken at the time closest to biopsy
- One study[400] included multiple PIIINP assays from serial assessments and multiple biopsies per patient in the analysis (with some biopsies counted more than once as they were paired with more than one PIIINP assay), and only included biopsies with PIIINP tests within 6 months before and 6 months after biopsy
- The final study[399] serially assessed PIIINP but classed participants as positive on biopsy or PIIINP if at least one of their tests was abnormal (but it is unclear how many abnormal test results they may also have had).

Two studies[399,402] had an unclear period of time between the measurement of the index test and the reference standard, which may have meant that the clinical condition of the individual had changed in the time that elapsed between the assessments.

One study[399] performed serial analyses of PIIINP and multiple biopsies per patient but did not include all of the PIIINP or biopsy results in the analysis; therefore, those who tested positive (based on at least one abnormal result) could also have had several negative tests. This study was still considered eligible for inclusion as those classed as negative would not have had even a single elevated PIIINP or abnormal biopsy result among the multiple test results, which is informative as we are interested in a screening test most able to accurately determine those who do not have liver abnormalities.

Results

Note that PIIINP elevation can be due to an increase in fibrosis (and so cleaving of pro-collagen) anywhere in the body. Therefore, in those with psoriasis and arthritis it is possible that any elevation in PIIINP is due to the arthritis rather than the liver. In the available studies the proportion with PsA ranged from 22-46%, but was unclear in two studies[392,401].

In one study[392] the range of PIIINP values in a control group of 11 people with PsA and no MTX exposure was 2.2-4.6 ng/ml.

In the study[400] with 22% PsA, 4 of 6 grade II biopsies from 4 patients with inflammatory arthritis had elevated PIIINP in all associated readings and the other two biopsies had some abnormal PIIINP readings.

In one pilot study[401] one out of 11 participants with PsA gave a false positive result, and this participant had steatosis on biopsy. This was the only false positive in the study. Note that in a sub-group analysis of 10 people with PsA and 13 people with psoriasis but no arthritic component the accuracy for ruling out was actually higher in the group with PsA (sensitivity 100% vs 33% and NPV 100% vs 40%); however, the sample sizes in the subgroups were very small.

In the final study[399] 38.6% had PsA and one of the two false positives was a participant with PsA.

Sensitivity and specificity: The findings for the sensitivity and specificity of PIIINP varied between the studies. The sensitivity ranged from 62.5 to 100% and specificity from 63.6 to 97.9%. Note that the sensitivity and specificity were high in the study with the highest risk of bias and the lowest prevalence[399], which did not include all of the PIIINP assay results in the analysis.

Positive predictive value/negative predictive value: If the PIIINP assay was positive the probability of having liver fibrosis or cirrhosis (PPV or proportion of patients with a positive test who are correctly diagnosed) ranged from 23.4 to 95.0% and if the scan was negative the probability of not having liver fibrosis or cirrhosis (NPV or proportion of patients with a negative test who are correctly diagnosed) ranged from 88.5 to 100% (0 to 11.5% chance of having fibrosis or cirrhosis despite having a negative test).

Given that the pre-test probabilities of having liver fibrosis or cirrhosis were 24.1, 5.8, 13.7 and 34.7% in the four populations, this means that the PIIINP assay improves the ability to determine a positive diagnosis (over and above the known prevalence) by 9.7 to 60.3% and a negative diagnosis by 5.6 to 23.2%. Note that the value-added PPV was markedly higher in the two Zachariae studies[399,402].

Likelihood ratio: A positive test result ranged from 1.93 to 36 times more likely in a person with compared to a person without fibrosis/cirrhosis, and a negative test result ranged from 1.79-times to infinitely more likely in a person without compared to a person with fibrosis/cirrhosis.

The two Zachariae studies[399,402] demonstrated markedly higher values for sensitivity and PPV than the other two studies.

Additional information

- One study[400] noted that three liver biopsies in two morbidly obese patients who also had maturity-onset diabetes were graded II on Roenigk classification but showed signs of NASH (rather than portal fibrosis, which is more often associated with MTX use).
- In one study[392] the three cases of cirrhosis were all correctly identified and the sensitivity and specificity for detecting fibrosis alone were 81% and 62%, respectively, based on one biopsy per patient.

12.1.334 Fibrotest and fibroscan

Methods

One study[403] was found that investigated the diagnostic accuracy of Fibrotest and Fibroscan in people with psoriasis eligible to receive methotrexate. The reference standard biopsy classification was based on the Metavir system and the definition of abnormal was Metavir >F2. The definition of abnormal on the Fibrotest was defined by a cut-off of 0.31 and on Fibroscan by a cut-off of 7.1kPa based on the literature.

This study did not state whether the population was based on a consecutive sample and there could have been up to 18 months between the index test and reference standard being undertaken, which could be long enough for the liver to develop fibrosis or cirrhosis. Additionally, for Fibroscan there was some discrepancy between the details in the text and the reported diagnostic accuracy statistics.

Results

Sensitivity and specificity: The sensitivity was 83% for Fibrotest and 50% for Fibroscan, while the specificities were 61% and 88%, respectively

Positive predictive value/negative predictive value: If the Fibrotest was positive the probability of having liver fibrosis or cirrhosis (PPV or proportion of patients with a positive test who are correctly diagnosed) was 42% and if the test was negative the probability of not having liver fibrosis or cirrhosis (NPV or proportion of patients with a negative test who are correctly diagnosed) was 92% (8% chance of having fibrosis or cirrhosis despite having a negative test). The PPV for Fibroscan was 33% while the NPV was 86% (14% chance of having fibrosis or cirrhosis despite having a negative test).

Given that the pre-test probability of having fibrosis/cirrhosis was 25% for the Fibrotest population, this means that the liver scan improves the ability to determine a positive diagnosis (over and above the known prevalence) by 16.7% and a negative diagnosis by 16.7%. It was not possible to calculate the valued-added predictive values for Fibroscan as the population sample used for the calculation of PPV and NPV was unclear.

Likelihood ratio**:** For Fibrotest, a positive test was 2.14-times more likely in a person with compared to a person without fibrosis/cirrhosis, and a negative test was 3.7-times more likely in a person without compared to a person with fibrosis/cirrhosis. Again, it was not possible to calculate this statistic for Fibroscan as the 2x2 table could not be verified.

Additional information

In nine patients, Fibroscan and Fibrotest resulted in different Metavir scores with a discordance of two stages. In four of them, the total Fibroscan procedure failed because of the presence of obesity. In the remaining five, biopsy length was significantly shorter than the biopsy length of the remaining patients.

12.114 Non-invasive liver tests vs. liver biopsy

12.1.421 Evidence profile

3 **Table 168: Modified GRADE profile for the diagnostic accuracy of tools to detect liver fibrosis or cirrhosis**

Study characteristics			Quality Assessment					Summary of findings					
No. of studies	Design	N	Limitation	Inconsistency	Indirectness	Imprecision*	Other consideration	Pre-test probability	Sensitivity	Specificity	Post-test probability positive (if positive result)	Post-test probability negative (if negative result)	Quality
LFTs vs biopsy													
AST													
Newman 1989	Retrospective	168	VS[a]	N[b]	N	N		Unclear for full group	20 (13-30)%	90 (84-93)%	49 (33-65)%	70 (62-76)%	⊕⊕OO LOW
O'Connor 1989	Retrospective	50 tests	S[c]	N[b]	N	VS	Pre-treatment	9.6%	40 (5-85)%	89 (76-96)%	29 (4-71)%	93 (81-99)%	⊕OOO VERY LOW
		47 (86 tests)	S[c]	N[b]	N	VS	Post-treatment	24.2%	43 (22-66)%	86 (75-93)%	50 (26-74)%	82 (71-91)%	⊕OOO VERY LOW
Paramsothy 1988	Prospective	15	VS[d]	N	N	VS		46.7%	29 (4-71)%	100 (63-100)%	100 (21-100)%	62%	⊕OOO VERY LOW
ALT													
Newman 1989	Retrospective	168	VS[a]	N[b]	N	S		Unclear for full group	5 (0.6-17)%	85 (72-94)%	22 (3-48)%	52 (40-63)%	⊕OOO VERY LOW
Ho 1986	Prospective	18	VS[e]	N	S[f]	VS	TH >32 U/l	27.8%	40 (7.9-71.3)%	84.6 (72.3-96.7)%	50 (9.8-89.2)%	78.6 (67.1-89.8)%	⊕OOO VERY LOW
			VS[5]	N	S[f]	VS	TH >40 U/l	27.8%	40 (8.0-58.9)%	92.3 (80.0-99.6)%	66.7 (13.4-98.2)%	80.0 (69.3-86.3)%	⊕OOO VERY LOW
Bilirubin													

Study characteristics			Quality Assessment					Summary of findings					
Newman 1989	Retrospective	168	VS[a]	N[b, g]	N	N	TH ≥2 µmol/l	Unclear for full group	19 (12-29)%	86 (80-90)%	41 (26-57)%	60 (63-75)%	⊕⊕OO LOW
O'Connor 1989	Retrospective	50 tests	S[c]	N[b, g]	N	VS	Pre-treatment	9.6%	20 (7-72)%	96 (85-99)%	33 (1-91)%	91 (80-98)%	⊕OOO VERY LOW
		47 (86 tests)	S[c]	N[b, g]	N	S	Post-treatment	24.2%	10 (2-30)%	95 (87-99)%	40 (5-85)%	76 (65-85)%	⊕⊕OO LOW
Paramsothy 1988	Prospective	15	VS[d]	N[g]	N	VS	TH ≥18 µmol/l	46.7%	0 (0-41)%	88 (47-100)%	0 (0-87)%	50 (41-58)%	⊕OOO VERY LOW
Alkaline phosphatase													
Newman 1989	Retrospective	168	VS[a]	N[b]	N	N		Unclear for full group	38 (28-49)%	71 (63-77)%	39 (28-49) %	70 (63-77) %	⊕⊕OO LOW
O'Connor 1989	Retrospective	50 tests	S[c]	N[b]	N	VS	Pre-treatment	9.6%	40 (5-85)%	77 (60-87)%	15 (2-45)%	92 (83-97)%	⊕OOO VERY LOW
		47 (86 tests)	S[c]	N[b]	N	S	Post-treatment	24.2%	57 (34-78)%	72 (60-83)%	40 (23-59)%	84 (72-92)%	⊕⊕OO LOW
Paramsothy 1988	Prospective	15	VS[d]	N	N	VS		46.7%	42.9 (14.1-65.6)%	75.0 (49.9-94.9)%	60.0 (19.8-91.9)%	60.0 (39.9-75.9)%	⊕OOO VERY LOW
Prothrombin time													
Newman 1989	Retrospective	168	VS[a]	N[b]	N	N		Unclear for full group	1 (0-5) %	99 (94-99) %	25 (6-80) %	66 (61-72) %	⊕⊕OO LOW
Albumin													
Newman 1989	Retrospective	168	VS[a]	N[b]	N	N	TH ≥35 g/l	Unclear for full group	19 (11-29)%	76 (68-83)%	33 (19-48) %	61 (52-68) %	⊕⊕OO LOW
Paramsothy 1988		15	VS[d]	N	N	VS	TH ≥150 u/l	46.7%	29 (4-71)%	100 (63-100)%	100 (21-100)%	62 %	⊕OOO VERY LOW
Gamma-glutamyl transferase													

Study characteristics			Quality Assessment					Summary of findings					
Paramsothy 1988	Prospective	15	VS[d]	N	N	VS		42.9%	33.3 (6.7-65.8)%	62.5 (42.5-86.8)%	40 (8.0-79.0)%	55.6 (37.8-77.2)%	⊕OOO VERY LOW
Galactose tolerance test													
Lenler-Peterson 1982 1989	Retrospective	45	VS[h]	N	S[i]	N		69.5%	14.3 (10.2-16.4)%	93.5 (84.1-98.3)%	83.3 (59.5-95.5)%	32.3 (29.1-34.0)%	⊕OOO VERY LOW
Scintigraphy vs biopsy													
Geronemus 1982	Retrospective	24	VS[j]	N[b, k]	N	VS		29.2%	57.1 (22.7-86.7)%	64.7 (50.5-76.9)%	40.0 (15.9-60.7)%	78.6 (61.3-93.3)%	⊕OOO VERY LOW
McHenry 1992	Retrospective	63	VS[l]	N[k, m]	N	S		6.9%	83.3 (38.0-99.1)%	81.5 (78.1-82.6)%	25.0 (11.4-29.7)%	98.5 (94.4-99.9)%	⊕OOO VERY LOW
Mitchell 1987	Prospective	49	VS[n]	N[k]	N	S		24.5%	50.0 (24.2-74.9)%	73.0 (64.6-81.1)%	37.5 (18.2-56.2)%	81.8 (72.4-90.9)%	⊕OOO VERY LOW
Ultrasound vs biopsy													
Mitchell 1987	Prospective	49	VS[n]	N[k]	N	VS		24.5%	0%	86%	0%	73%	⊕OOO VERY LOW
Coulson 1987	Prospective	28	S[o]	N[k]	N	S	Any fibrosis	48.2%	19.0 (7-39)%	100 (88-100)%	100 (39-100)%	57%	⊕⊕OO LOW
			S[o]	N[k, m]	N	VS	Portal fibrosis	37.0%	25.0 (9-49)%	100.0 (90-100)%	100% (39-100)%	69%	⊕OOO VERY LOW
PIIINP vs biopsy													
Boffa 1996	Prospective	87	S[o]	N	N	N	Paired tests	24.1%	81.0 (60.3-93.5)%	63.6 (57.1-67.6)%	41.5 (30.9-47.9)%	91.3 (81.9-97.0)%	⊕⊕⊕O MODERATE
Zachariae	Retrospective	70	VS[p]	N	S[q]	VS	Serial	5.8%	100 (40-100)%	97 (89-100)%	66 (30-84)%	100%	⊕OOO

Study characteristics			Quality Assessment					Summary of findings					
2001							PIIINP assays						VERY LOW
Maurice 2005	Retrospective	34	S[r]	N[b]	N[s]	N	Serial PIIINP assays	13.7%	62.5 (42.1-79.8)%	67.5 (64.3-70.3)%	23.4 (15.8-29.9)%	91.9 (87.5-95.6)%	⊕⊕⊕O MODERATE
Zachariae 1989 and Risteli 1988	Prospective	73	VS[t]	N	N	N	Paired tests	34.7%	76.0 (61.8-79.8)%	97.9 (90.3-99.9)%	95.0 (77.2-99.7)%	88.5 (81.6-90.3)%	⊕⊕OO LOW
		13	VS[u]	N	N	VS	No-PsA	69.2%	33.0 (7.0-70)%	100 (40-100)%	100 (33-100)%	40%	⊕OOO VERY LOW
		10	VS[u]	N	N	VS	PsA	40%	100 (40-100)%	83 (36-100)%	80 (40-92)%	100%	⊕OOO VERY LOW
Fibrotest													
Berends 2007	Retrospective	24	S[v]	N	N[w]	VS		25%	83.3 (40.8-99.1)%	61.1 (46.9-66.4)%	41.7 (20.4-49.6)%	91.7 (70.4-99.6)%	⊕OOO VERY LOW
Fibroscan													
Berends 2007	Retrospective	24	VS[x]	N	N[w]	VS[y]		25%	50 (0.07-0.93)%	88 (0.62-0.98)%	33%	86%	⊕OOO VERY LOW

**Imprecision is assessed based on the sensitivity, specificity PPV and NPV of the tests; if there was no majority in the assessment of imprecision across these statistics higher weighting was given to sensitivity and NPV as these are most important for the intended role of the test.*

(a) Unclear threshold selection; unclear if all patients included in the analysis or received both tests; experience of pathologist and adequacy of biopsy specimen unclear
(b) Note that biopsy grading was according to Roenigk (threshold does not include fibrous expansion of portal tracts without extension to the parenchyma and fibrosis not associated with the portal tracts is not scored at all; therefore, NAFLD which may be associated with MTX use will not be detected on this score)
(c) Unclear sampling and unclear baseline characteristics; not all patients were included in the analysis due to incomplete data sets/not receiving both tests; experience of pathologist and adequacy of biopsy specimen unclear
(d) Unclear sampling; unclear time between tests; experience of pathologist and adequacy of biopsy specimen unclear
(e) Unclear patient selection method; unclear time between tests; experience of pathologist and adequacy of biopsy specimen unclear
(f) Only included those with an indication of liver damage (either by cumulative dose of methotrexate or raised ALT levels)
(g) Thresholds for abnormal enzyme test varied between studies
(h) Unclear baseline characteristics; time between tests unclear; unclear if biopsy assessed blinded to clinical and laboratory data; experience of pathologist and adequacy of biopsy specimen unclear

(i) Population limited to those known to have developed fibrosis or cirrhosis
(j) Unclear if selection was based on a consecutive sample; unclear if tests were interpreted by blinded assessors and unclear who made the assessments; adequacy of biopsy specimen unclear
(k) Definition of abnormal result on scan varies between studies
(l) Adequacy of biopsy specimen unclear
(m) Note that the threshold biopsy grading for abnormal reference test result was at least moderate fibrosis, which corresponded to portal fibrosis consistent with Roenigk grade III
(n) Unclear if selection was based on a consecutive sample; unclear if tests were interpreted by blinded assessors and experience of pathologist assessing biopsy unclear; adequacy of biopsy specimen unclear
(o) Unclear if selection was based on a consecutive sample; experience of biopsy assessor and adequacy of biopsy specimen unclear
(p) Unclear if selection was based on a consecutive sample; experience of biopsy assessor and adequacy of biopsy specimen unclear; unclear blinding of biopsy assessor and unclear order of tests
(q) Serial analyses of PIIINP were performed; therefore not a 1:1 relationship with biopsies. Those who tested positive on either test could also have had several negative tests
(r) Experience of biopsy assessor and adequacy of biopsy specimen unclear
(s) Serial analyses of PIIINP were performed; therefore not a 1:1 relationship with biopsies but data on all assays included (so some biopsies were counted more than once as paired with multiple PIIINP assay results)
(t) Unclear if selection was based on a consecutive sample; experience of biopsy assessor and adequacy of biopsy specimen unclear; unclear order and timing between tests
(u) Subgroup analysis of pilot group only; unclear if selection was based on a consecutive sample; experience of biopsy assessor and adequacy of biopsy specimen unclear; unclear order and timing between tests
(v) Unclear if selection was based on a consecutive sample; maximum time between tests was 18 months
(w) Biopsy grading was classed as abnormal if it was Metavir grade F2 or greater (threshold does not include fibrous expansion of portal tracts without septa and fibrosis not associated with the portal tracts is not scored at all, similar to the Roenigk score)
(x) Unclear if selection was based on a consecutive sample; maximum time between tests was 18 months; uncertainty in how the diagnostic test accuracy statistics were calculated (unable to reconcile with 2x2 table)
(y) No estimate of imprecision available from the paper

12.1.252 Evidence summary

Table 169: Summary statistics for diagnostic accuracy of tools for fibrosis and cirrhosis

Study	N	Index test threshold	Reference test threshold	Pre-test probability	Sensitivity	Specificity	PPV *Value-added PPV*	NPV *Value-added NPV*	Post-test probability of PsA despite test –ve	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
LFTs vs biopsy											
AST											
Newman 1989	168	≥40 U/L	Roenigk grade 3-4	Unclear for full group	20 (13-30)%	90 (84-93)%	49 (33-65)%	70 (62-76)%	30%	NA	NA

Study	N	Index test threshold	Reference test threshold	Pre-test probability	Sensitivity	Specificity	PPV *Value-added PPV*	NPV *Value-added NPV*	Post-test probability of PsA despite test –ve	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
O'Connor 1989 – pre-treatment	50	Unclear (based on 'normal ranges')	Roenigk grade 3-4	9.6%	40 (5-85)%	89 (76-96)%	29 (4-71)% *19.4%*	93 (81-99)% *2.6%*	7%	3.76 (0.97-15)	0.67 (0.33-1.38)
O'Connor 1989 – post-treatment	47 (86 tests)	Unclear (based on 'normal ranges')	Roenigk grade 3-4	24.2%	43 (22-66)%	86 (75-93)%	50 (26-74)% *25.8%*	82 (71-91)% *6.2%*	18%	3.13 (1.49-6.56)	0.66 (0.45-0.95)
Paramsothy 1988	15	≥40 U/L	Fibrosis (any severity)	46.7%	29%	100%	100 (21-100)% *53.3%*	62% *8.7%*	38%	Infinity (0.31-101)	0.71 (0.44-1.19)
ALT											
Newman 1989	168	≥40 U/L	Roenigk grade 3-4	Unclear for full group	5 (0.6-17)%	85 (72-94)%	22 (3-48)%	52 (40-63)%	48%	NA	NA
Ho 1986	18	>32 U/L *As defined in study*	Fibrosis (septum formation)	27.8%	40 (7.9-71.3)%	84.6 (72.3-96.7)%	50 (9.8-89.2)% *22.2%*	78.6 (67.1-89.8)% *6.4%*	21.4%	2.60 (0.49-14)	0.71 (0.33-1.50)
		>40 U/L *consistent with other studies*	Fibrosis (septum formation)	27.8%	40 (8.0-58.9)%	92.3 (80.0-99.6)%	66.7 (13.4-98.2)% *38.9%*	80.0 (69.3-86.3)% *7.8%*	20.0%	5.20 (0.60-45)	0.65 (0.31-1.35)
Bilirubin											
Newman 1989	168	≥2 µmol/l	Roenigk grade 3-4	Unclear for full group	19 (12-29)%	86 (80-90)%	41 (26-57)%	60 (63-75)%	40%	NA	NA
O'Connor 1989 –	50	Unclear (based on	Roenigk grade 3-4	9.6%	20 (7-72)%	96 (85-99)%	33 (1-91)% *23.4%*	91 (80-98)% *0.6%*	9%	4.7 (0.51-43)	0.84 (0.54-

Study	N	Index test threshold	Reference test threshold	Pre-test probability	Sensitivity	Specificity	PPV *Value-added PPV*	NPV *Value-added NPV*	Post-test probability of PsA despite test –ve	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
pre-treatment		'normal ranges')									1.30)
O'Connor 1989 – post-treatment	47 (86 tests)	Unclear (based on 'normal ranges')	Roenigk grade 3-4	24.2%	10 (2-30)%	95 (87-99)%	40 (5-85)% *15.8%*	76 (65-85)% *0.2%*	24%	1.57 (0.31-8.00)	0.97 (0.84-1.11)
Paramsothy 1988	15	≥18 µmol/l	Fibrosis (any severity)	46.7%	0%	88%	0 (0-87)% *-46.7%*	50 (41-58)% *-3.3%*	50%	0	1.14 (0.80-1.58)
Alkaline phosphatase											
Newman 1989	168	≥100 U/L	Roenigk grade 3-4	Unclear for full group	38 (28-49)%	71 (63-77)%	39 (28-49) %	70 (63-77) %	30%	NA	NA
O'Connor 1989 – pre-treatment	50	Unclear (based on 'normal ranges')	Roenigk grade 3-4	9.6%	40 (5-85)%	77 (60-87)%	15 (2-45)% *5.4%*	92 (83-97)% *1.6%*	8%	1.71 (0.52-5.63)	0.78 (0.38-1.63)
O'Connor 1989 – post-treatment	47 (86 tests)	Unclear (based on 'normal ranges')	Roenigk grade 3-4	24.2%	57 (34-78)%	72 (60-83)%	40 (23-59)% *15.8%*	84 (72-92)% *8.2%*	16%	2.03 (1.21-3.41)	0.6 (0.37-0.98)
Paramsothy 1988	15	≥121 u/l	Fibrosis (any severity)	46.7%	42.9 (14.1-65.6)%	75.0 (49.9-94.9)%	60.0 (19.8-91.9)% *13.3%*	60.0 (39.9-75.9)% *6.7%*	40.0%	1.71 (0.39-7.48)	0.76 (0.36-1.62)
Prothrombin time											
Newman 1989	168	≥14.5 s	Roenigk grade 3-4	Unclear for full group	1 (0-5) %	99 (94-99) %	25 (6-80) %	66 (61-72) %	34%	NA	NA
Albumin											
Newman	168	≥35 g/l	Roenigk	Unclear for	19 (11-29)%	76 (68-83)%	33 (19-48) %	61 (52-68) %	39%	NA	NA

Study	N	Index test threshold	Reference test threshold	Pre-test probability	Sensitivity	Specificity	PPV *Value-added PPV*	NPV *Value-added NPV*	Post-test probability of PsA despite test –ve	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
1989			grade 3-4	full group							
Paramsothy 1988	15	≥150 u/l	Fibrosis (any severity)	46.7%	29%	100%	100 (21-100)% *53.3%*	62 % *8.7%*	38%	Infinity (0.31-101)	0.71 (0.44-1.19)
Gamma-glutamyl transferase											
Paramsothy 1988	15	≥36 u/l	Fibrosis (any severity)	42.9%	33.3 (6.7-65.8)%	62.5 (42.5-86.8)%	40 (8.0-79.0)% *-2.9%*	55.6 (37.8-77.2)% *-1.5%*	44.4%	0.89 (0.21-3.76)	1.07 (0.49-2.33)
Galactose tolerance test											
Lenler-Peterson 1982 1989	45 (151 concurrent test)	≥3 g/l	Fibrosis (unclear classification)	69.5%	14.3 (10.2-16.4)%	93.5 (84.1-98.3)%	83.3 (59.5-95.5)% *13.8%*	32.3 (29.1-34.0)% *1.8%*	67.7%	2.19 (0.67-7.20)	0.92 (0.82-1.02)
Scintigraphy vs biopsy											
Geronemus 1982	24	Presence of abnormalities[(a)]	Roenigk grade 3-4	29.2%	57.1 (22.7-86.7)%	64.7 (50.5-76.9)%	40.0 (15.9-60.7)% *10.8%*	78.6 (61.3-93.3)% *7.8%*	21.4%	1.62 (0.65-4.02)	0.66 (0.26-1.67)
McHenry 1992	63 (87 paired results)	Portal contribution <50%	Portal fibrosis	6.9%	83.3 (38.0-99.1)%	81.5 (78.1-82.6)%	25.0 (11.4-29.7)% *18.8%*	98.5 (94.4-99.9)% *5.4%*	1.5%	4.50 (2.52-8.04)	0.20 (0.03-1.23)
Mitchell 1987	49	Presence of abnormalities[(b)]	Fibrosis (any severity)	24.5%	50.0 (24.2-74.9)%	73.0 (64.6-81.1)%	37.5 (18.2-56.2)% *13.0%*	81.8 (72.4-90.9)% *5.3%*	19.2%	1.85 (0.85-4.02)	0.69 (0.38-1.25)
Ultrasound vs biopsy											
Mitchell 1987	49	Presence of	Fibrosis (any severity)	24.5%	0%	86%	0% *-24.5%*	73% *-2.5%*	27%	0	1.16 (0.95-

Study	N	Index test threshold	Reference test threshold	Pre-test probability	Sensitivity	Specificity	PPV *Value-added PPV*	NPV *Value-added NPV*	Post-test probability of PsA despite test –ve	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
		abnormalities[c]									1.33)
Coulson 1987	28 (58 paired observations)	Presence of abnormalities[d]	Fibrosis (any severity)	48.2%	19.0%	100%	100 (39-100)% *51.8%*	57% *5.2%*	43%	Infinity (0.69-204)	0.81 (0.67-0.99)
			Fibrosis (at least moderate – portal fibrosis[e])	37.0%	25.0%	100.0%	100% (39-100)% *63.0%*	69% *6.0%*	31%	Infinity (1.07-315)	0.75 (0.58-0.97)
PIIINP vs biopsy											
Boffa 1996	87 (147 paired tests)	>4.2 ng/ml	Fibrosis	24.1%	81.0 (60.3-93.5)%	63.6 (57.1-67.6)%	41.5 (30.9-47.9)% *17.4%*	91.3 (81.9-97.0)% *15.4%*	8.7%	2.23 (1.52-3.26)	0.30 (0.12-0.74)
Zachariae 2001	70 (189 biopsies and 329 assays)	>4.2 ng/ml	Fibrosis (any severity)	5.8%	100%	97%	66 (30-84)% *60.2%*	100% *5.8%*	0%	32 (6.80-83)	0 (0.01-1.44)
Maurice 2005	34 (70 biopsies and 306 assays)	>4.2 ng/ml	Roenigk grade 3-4	13.7%	62.5 (42.1-79.8)%	67.5 (64.3-70.3)%	23.4 (15.8-29.9)% *9.7%*	91.9 (87.5-95.6)% *5.6%*	8.1%	1.93 (1.31-2.83)	0.56 (0.33-0.94)
Zachariae 1989 and Risteli 1982	73	>4.2 ng/ml	Fibrosis (any severity)	34.7%	76.0 (61.8-79.8)%	97.9 (90.3-99.9)%	95.0 (77.2-99.7)% *60.3%*	88.5 (81.6-90.3)% *23.2%*	11.5%	36 (5.07-251)	0.25 (0.12-0.49)
Risteli	13	>4.2	Fibrosis (any	69.2%	33.0 (7.0-70)%	100 (40-100)%	100 (33-	40%	60%	Infinity	0.67

Study	N	Index test threshold	Reference test threshold	Pre-test probability	Sensitivity	Specificity	PPV *Value-added PPV*	NPV *Value-added NPV*	Post-test probability of PsA despite test –ve	Positive likelihood ratio (LR+)	Negative likelihood ratio (LR-)
1982 – no PsA subgroup		ng/ml	severity)				100)% *30.8%*	*9.2%*			
Risteli 1982 –PsA subgroup	10	>4.2 ng/ml	Fibrosis (any severity)	40%	100 (40-100)%	83 (36-100)%	80 (40-92)% *40%*	100% *40%*	0%	6.00 (0.99,18)	0.00 [0.01,1.82)
Fibrotest											
Berends 2007	24	>0.31	≥F2 on Metavir system	25%	83.3 (40.8-99.1)%	61.1 (46.9-66.4)%	41.7 (20.4-49.6)% *16.7%*	91.7 (70.4-99.6)% *16.7%*	8.3%	2.14 (1.08,4.23)	0.27 (0.04,1.69)
Fibroscan											
Berends 2007	24	>7.1 kPa	≥F2 on Metavir system	25% (20% of those assessable)	50%	88%	33% *?*	86% *?*	14%	-	-

NA: Not available
NPV: Negative predictive value
PPV: Positive predictive value
(a) The abnormalities assessed were heterogeneous uptake, hepatomegaly, extra hepatic uptake and focal defects
(b) The abnormalities assessed were size of liver and spleen, pattern of uptake in these organs and degree of extrahepatic uptake
(c) The abnormalities assessed were liver size, shape, echo pattern and information about the biliary and vascular system according to a standard proforma
(d) The abnormalities assessed were fatty change and fibrosis; only those showing fibrosis were counted as positive tests
(e) This is in accordance with Roenigk criteria

12.1.413 Evidence statements

The following statements are organised by outcome and ordered to list the tests in approximate order from the best to the worst diagnostic accuracy according to that measure.

Sensitivity: of patients with fibrosis or cirrhosis on biopsy, the proportion expected to test positive

- PIIINP: 62.5 to 100% [4 studies; 264 participants; moderate to very low quality evidence][392,399,400,402]
- Scintigraphy (portal contribution): 83% [1 study; 63 participants; very low quality evidence]
- Fibrotest: 83% [1 study; 24 participants; very low quality evidence][403]
- Scintigraphy (abnormalities): 50-57% [2 studies; 73 participants; very low quality evidence][395,397]
- AP: 38-57% [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Fibroscan: 50% [1 study; 24 participants; very low quality evidence][403]
- AST: 20-43% [3 studies; 235 participants; low to very low quality evidence][298,371,372]
- Gamma-glutamyl transferase: 33% [1 study; 15 participants; very low quality evidence][298]
- ALT: 5-40% [2 studies; 186 participants; very low quality evidence][371,393]
- Ultrasound (portal fibrosis): 25% [1 study; 28 participants; very low quality evidence][398]
- Albumin: 19-29% [2 studies; 183 participants; low to very low quality evidence][298,371]
- Bilirubin: 0-20% [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Ultrasound (any fibrosis): 0 to 19% [2 studies; 77 participants; low to very low quality evidence][397,398]
- Galactose: 14% [1 study; 45 participants; very low quality evidence][394]
- Prothrombin time: 1% [1 study; 168 participants; low quality evidence][371]

Specificity: of patients without fibrosis or cirrhosis on biopsy, the proportion expected to test negative

- Ultrasound (portal fibrosis): 100% [1 study; 28 participants; very low quality evidence][398]
- Prothrombin time: 99% [1 study; 168 participants; low quality evidence][371]
- Ultrasound (any fibrosis): 86 to 100% [2 studies; 77 participants; low to very low quality evidence][397,398]
- AST: 86-100% [3 studies; 235 participants; low to very low quality evidence][298,372]
- Bilirubin: 86-96% [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Galactose: 94% [1 study; 45 participants; very low quality evidence][394]
- ALT: 85-92% [2 studies; 186 participants; very low quality evidence][371,393]
- Albumin: 76-100% [2 studies; 183 participants; low to very low quality evidence][298,371]
- Fibroscan: 88% [1 study; 24 participants; very low quality evidence][403]
- Scintigraphy (portal contribution): 82% [1 study; 63 participants; very low quality evidence]
- PIIINP: 63.6 to 97.9% [4 studies; 264 participants; moderate to very low quality evidence][392,399,400,402]
- Alkaline phosphatase: 71-77% [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Scintigraphy (abnormalities): 65-73% [2 studies; 73 participants; very low quality evidence][395,397]
- Gamma-glutamyl transferase: 63% [1 study; 15 participants; very low quality evidence][298]
- Fibrotest: 61.1% [1 study; 24 participants; very low quality evidence][403]

Positive predictive value (figure in brackets is value-added PPV; the improvement in ability to determine a positive diagnosis over and above the known prevalence): if the liver function test was positive the probability of having liver fibrosis or cirrhosis (PPV) was:

- Galactose: 83% (13.8%) [1 study; 45 participants; very low quality evidence][394]
- Albumin: 33-100% (53%) [2 studies; 183 participants; low to very low quality evidence][298,371]
- AST: 29-100% (19-53%) [3 studies; 235 participants; low to very low quality evidence][298,372]
- PIIINP: 23.4 to 95.0% (9.7 to 60.3%) [4 studies; 264 participants; moderate to very low quality evidence][392,399,400,402]
- ALT: 22-67% (22-39%) [2 studies; 186 participants; low to very low quality evidence][371,393]
- AP: 15-60% (5.4 to 16%) [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Fibrotest: 42% (16.7%) [1 study; 24 participants; very low quality evidence][403]
- GGT: 40% (-2.9%) [1 study; 15 participants; very low quality evidence][298]
- Scintigraphy (abnormalities): 37.5-40.0% (10.8 to 13.0%) [2 studies; 73 participants; very low quality evidence][395,397]
- Bilirubin: 0-41% (-47 to 23%) [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Fibroscan: 33% (NA) [1 study; 24 participants; very low quality evidence][403]
- Scintigraphy (portal contribution): 25% (18.8 %) [1 study; 63 participants; very low quality evidence][396]
- Prothrombin time: 25% (NA) [1 study; 168 participants; low quality evidence][371]
- Ultrasound: 0 to 100% (-24.5 to 63.0%) [2 studies; 77 participants; low to very low quality evidence][397,398]

Negative predictive value (figure in brackets is value-added NPV; the improvement in ability to determine a negative diagnosis over and above the known prevalence): if the liver function test was negative the probability of not having liver fibrosis or cirrhosis (NPV) was:

- PIIINP: 88.5 to 100% (5.6 to 23.2%) [4 studies; 264 participants; moderate to very low quality evidence][392,399,400,402]
- Scintigraphy (portal contribution): 98.5% (5.4%) [3 studies; 63 participants; very low quality evidence][396]
- Fibrotest: 92% (16.7%) [1 study; 24 participants; very low quality evidence][403]
- Fibroscan: 86% (NA) [1 study; 24 participants; very low quality evidence][403]
- Scintigraphy (abnormalities): 78.6 to 81.8% (5.3 to 7.8%) [2 studies; 73 participants; very low quality evidence][395,397]
- AST: 62-93% (2.6 to 8.7%) [3 studies; 235 participants; low to very low quality evidence][298,372]
- AP: 60-92% (1.6 to 8.2%) [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Bilirubin: 50-91% (-3.3 to 0.6%) [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- ALT: 52-80% (6.4-7.8%) [2 studies; 186 participants; very low quality evidence][371,393]
- Ultrasound: 57 to 73% (-2.5 to 6.0%) [2 studies; 77 participants; low to very low quality evidence][397,398]
- Prothrombin time: 66% (NA) [1 study; 168 participants; low quality evidence][371]
- Albumin: 61-62% (8.7%) [2 studies; 183 participants; low to very low quality evidence][298,371]
- Gamma-glutamyl transferase: 56% (-1.5%) [1 study; 15 participants; very low quality evidence][298]
- Galactose: 32% (1.8%) [1 study; 45 participants; very low quality evidence][394]

Positive likelihood ratio: in a person with compared to a person without liver fibrosis or cirrhosis, the number of times more likely a positive test result is:

- Albumin: infinity [2 studies; 183 participants; low to very low quality evidence][298,371]
- AST: 3.13-infintiy [3 studies; 235 participants; low to very low quality evidence][298,372]
- PIIINP: 1.93 to 36 [4 studies; 264 participants; moderate to very low quality evidence][392,399,400,402]
- Scintigraphy (portal contribution): 4.50 [1 study; 63 participants; very low quality evidence]
- Ultrasound: zero to infinite [2 studies; 77 participants; low to very low quality evidence][397,398]
- ALT: 2.6-5.2 [2 studies; 186 participants; very low quality evidence][371,393]
- Bilirubin: 1.57-4.7 [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Galactose: 2.19 [1 study; 45 participants; very low quality evidence][394]
- Fibrotest: 2.14 [1 study; 24 participants; very low quality evidence][403]
- Alkaline phosphatase: 1.71-2.03 [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Scintigraphy (abnormalities): 1.62 to 1.85 [2 studies; 73 participants; very low quality evidence][395,397]
- Gamma-glutamyl transferase: 0.89 [1 study; 15 participants; very low quality evidence][298]

Negative likelihood ratio: in a person without compared to a person with liver fibrosis or cirrhosis, the number of times more likely a negative test result is:

- Scintigraphy (portal contribution): 5.0 [1 study; 63 participants; very low quality evidence]
- PIIINP: 1.79-times to infinitely [4 studies; 264 participants; moderate to very low quality evidence][392,399,400,402]
- Fibrotest: 3.7 [1 study; 24 participants; very low quality evidence][403]
- Alkaline phosphatase: 1.3-1.7 [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- AST: 1.4-1.5 [3 studies; 235 participants; low to very low quality evidence][298,372]
- ALT: 1.4-1.5 [2 studies; 186 participants; very low quality evidence][371,393]
- Scintigraphy (abnormalities): 1.4 to 1.5 [2 studies; 73 participants; very low quality evidence][395,397]
- Albumin: 1.4 [2 studies; 183 participants; low to very low quality evidence][298,371]
- Galactose: 1.1 [1 study; 45 participants; very low quality evidence][394]
- Bilirubin: 0.88-1.2 [3 studies; 200 participants; low to very low quality evidence][298,371,372]
- Gamma-glutamyl transferase: 0.93 [1 study; 15 participants; very low quality evidence][298]
- Ultrasound: 0.86 to 1.2 [2 studies; 77 participants; low to very low quality evidence][397,398]

Conclusions

- The available studies mainly have small samples, which, combined with the relatively low prevalence of fibrosis and cirrhosis, mean that the estimates of diagnostic accuracy are imprecise, leading to uncertainty (particularly around the sensitivity of the tests)
- All of the tests generally perform better in terms of specificity compared with sensitivity, meaning that they are of greater value for confidently ruling in a diagnosis of clinically significant liver damage if the non-invasive test is positive, but there is less certainty that those who test negative actually do not have fibrosis or cirrhosis
- Ruling in a diagnosis:

- The specificity was consistently over 75% for the majority of the tests (ultrasound, prothrombin time, AST, bilirubin, galactose, ALT, albumin and scintigraphy when abnormality was assessed using the % portal contribution to total hepatic uptake of colloid and Fibroscan)
- However, there was great variability in the PPV for each test, with no test showing values consistently above 50% across the different studies (except the galactose tolerance test which was only assessed in one study[394])
- The positive likelihood ratio was best for AST, albumin, ultrasound and PIIINP

- Ruling out a diagnosis:
  - Accepting the uncertainty, the tests that may give a useful level of sensitivity are PIIINP, scintigraphy for detecting portal fibrosis and Fibrotest
  - Similarly, the NPV was only consistently over 75% for PIIINP, scintigraphy, Fibrotest and Fibroscan
  - The negative likelihood ratio was best for PIIINP, scintigraphy for detecting portal fibrosis and Fibrotest.

12.1.5 Economic evidence

One study[404] was included that evaluated different methods of monitoring for hepatotoxicity in people with psoriasis being treated with methotrexate. The methods Chalmers and colleagues evaluated were serial PIIINP testing with selective liver biopsy compared with routine liver biopsy. This study is summarised in the economic evidence profile below (Table 170 and Table 171). See also the full study evidence tables in Appendix I.

No relevant economic evaluations comparing other non-invasive liver monitoring methods were identified. No studies were excluded.

Table 170: Serial PIIINP versus routine liver biopsy – Economic study characteristics

Study	Limitations	Applicability	Other comments
Chalmers 2005	Very serious limitations (g)	Partially applicable (h)	• Cost analysis conducted alongside a multicentre prospective audit in UK and Ireland • Costs included biopsy, overnight hospital stay, histology, PIIINP analysis

(g) Given that treatment with methotrexate may continue for more than 2 years, time horizon may be insufficient. Does not report incidence of adverse events/ complications associated with liver biopsy and any effect on costs. Within trial analysis and so does not incorporate all available evidence on differences between monitoring methods but results appear consistent with results of clinical review.

(h) QALYs not used (cost consequence analysis).

The monitoring strategies evaluated by Chalmers and colleagues were defined as follows:

Serial PIIINP testing with selective liver biopsy:

- Where possible serum should be collected for PIIINP measurement prior to starting methotrexate. It should subsequently be measured every 2-3 months during continued treatment. Indications for considering liver biopsy:
  - Elevation of pretreatment PIIINP above 8.0 μg L^{-1}
  - Elevation of PIIINP above the normal range (1.7 to 4.2 μg L^{-1}) in at least three samples over a 12 month period
  - Elevation of PIIINP above 8.0 μg L^{-1} in two consecutive samples
- Indications for considering withdrawal of methotrexate:

- Elevation of PIIINP above 10.0 µg L^{-1} in at least three samples over a 12 months period

- The decision whether to perform liver biopsy, withdraw treatment or continue treatment despite raised PIIINP levels must also take into account other factors such as disease severity, patient age and the ease with which alternative therapies may be used in place of methotrexate.

Routine liver biopsy:

- In patients without risk factors for liver damage, perform first liver biopsy after cumulative dose of 1.0 to 1.5 g methotrexate
- Provided no significant abnormalities are found, repeat liver biopsy after each additional 1.5 g methotrexate
- When cumulate dose >4.0 g, perform biopsy after each additional 1.0 g methotrexate
- In patient with risk factors for liver damage, perform liver biopsy within 2-4 months of starting methotrexate and after each additional 0.5 to 1.0 g thereafter.

Table 171: Serial PIIINP versus routine liver biopsy – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Chalmers 2005	£25 (a)	Fewer liver biopsies per patient per year; fewer normal biopsies	PIIINP is more costly, but reduces number of biopsies (normal and abnormal) performed	Whether serial PIIINP with selective liver biopsy was more or less costly than routine liver biopsy was dependent on the unit cost of liver biopsy
Chalmers 2005	- £49 (b)		PIIINP is less costly and reduces number of biopsies (normal and abnormal) performed	

(a) Where PIIINP measurement costs £22.50 and liver biopsy costs £270.00 (Essex)
(b) Where PIIINP measurement costs £22.50 and liver biopsy costs £577.00 (Manchester)

Based on the findings of the study and if PIIINP measurement cost £22.50:

- Monitoring with serial PIIINP and selective liver biopsy is likely to be cost-saving if liver biopsy costs more than £375
- Monitoring with serial PIIINP and selective liver biopsy may be more costly if liver biopsy costs less than £375.

None of these cost estimates take into account the additional costs of managing potential complications of liver biopsy. With the risk of developing significant hepatic injury from liver biopsy being approximately 1-2% and the risk of mortality being around 0.01-0.1%, these costs (and impact on health-related quality of life) could be significant. If these costs were included, it is likely that cost of liver biopsy at which monitoring with serial PIIINP becomes cost-saving would be much lower. Table 172 below shows that the current cost of liver biopsy (excluding cost of potential complications) is between £553 for a day case and £816 for patients requiring an overnight stay in hospital.

In the event that a monitoring strategy of serial PIIINP measurement with selective liver biopsy is more costly than routine liver biopsy, the additional costs could be justified by improved health outcomes in terms of mortality and morbidity avoided. These would have to be weighed against the risk that some patients with significant liver abnormalities may be missed.

The authors investigated whether changing the threshold value upon which PIIINP was counted as predictive of liver fibrosis would increase the specificity of the test. They found that altering the threshold from 4.2 to 4.9 µg L^{-1} would have reduced the number of false positives (e.g. those

undergoing a liver biopsy who turn out to have normal result or minor abnormalities) by more than half, but at the risk of failing to identify patients with significant liver damage (e.g. false negatives).

The study does not indicate whether any significant abnormalities were missed in the serial PIIINP strategy and what the consequences for these patients might be. The authors assert that the risk of serious harm from liver biopsy outweighs the risk of missing significant liver damage in patients monitored using serial PIIINP.

12.176 Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 172: Unit costs of monitoring tests – exclusive of labour costs

Item	Unit Cost	Notes
Liver function tests	£4.12 per batch	Shepherd and colleagues 2006[405]
Liver scintigraphy	£180?	HRG RA36Z (Nuclear medicine – category 2) Other categories range from £170 to £700
Liver ultrasound	£53	HRG RA23Z; average of outpatient, direct access and other categories of care
PIIINP	£21.64	Woolacott and colleagues 2006[276]
Liver biopsy	Elective inpatient: £816 Day case: £553	HRG GB04Z; NHS Reference Costs

Source: NHS Reference Costs 2009-10[277]

12.177 Evidence statements

- One partially applicable cost-consequence analysis with very serious limitations found that for patients with psoriasis undergoing treatment with methotrexate, a strategy of monitoring hepatotoxicity with serial PIIINP and selective liver biopsy was likely to be cost saving compared to routine liver biopsy if the unit cost of liver biopsy was greater than £375.

12.2 Linking evidence to recommendations

Recommendations on methotrexate and monitoring for hepatotoxicity	**91. Before and during methotrexate treatment, evaluate for potential hepatotoxicity.** **92. Use standard liver function tests and serial serum procollagen III levels to monitor for abnormalities during treatment with methotrexate, taking into account pre-existing risk factors (for example obesity, diabetes and alcohol use), baseline results and trends over time.** **93. When using serum procollagen III levels to exclude liver fibrosis or cirrhosis, be aware that the:** • **test cannot be used in children** • **results may be unreliable in people with psoriatic arthritis**

	• **positive predictive value is 23–95% and the negative predictive value is 89–100%.** **94. Provide advice on modifiable risk factors for liver disease prior to and during therapy including alcohol intake and weight reduction if appropriate. For more information see 'Alcohol-use disorders: physical complications' (NICE clinical guideline 100), 'Alcohol-use disorders: preventing the development of hazardous and harmful drinking' (NICE public health guidance 24) and 'Obesity' (NICE clinical guideline 43).** **95. Seek timely specialist advice and consider referral to a clinician with expertise in liver disease if the results of liver tests are abnormal.**
Future research recommendations	**23. What is the clinical utility and validity of non-invasive markers of liver fibrosis in people with psoriasis receiving methotrexate or other treatment interventions?**
Relative values of different outcomes	Standard accuracy outcomes for diagnostic tests were looked for: • Sensitivity and specificity • Positive predictive value (PPV) • Negative predictive value (NPV) • Likelihood ratios. The GDG felt the most important characteristics of a test for dermatology use (i.e. for use as a screening test) are: • Very good accuracy to rule out those who do not have liver damage and refer all who may have the disease for specialist hepatology assessment, so that no true cases are missed (high sensitivity, NPV and LR-). • Reasonable accuracy for ruling in a diagnosis, to avoid wasting resources by making inappropriate referrals to hepatology (specificity, PPV and LR+). The test should also be practical for use in a dermatology setting.
Trade off between clinical benefits and harms	• The GDG agreed not to recommend scintigraphy on the grounds that it is impractical and involves a radioactive isotope.
Economic considerations	Limited evidence was available to inform the GDG about the cost-effectiveness of alternative methods for monitoring hepatotoxicity associated with methotrexate treatment. One costing study showed that serial testing with PIIINP and selective liver biopsy was likely to be cost saving compared to routine liver biopsy if the cost of liver biopsy was less than £375. NHS reference costs from 2009-10 indicate that liver biopsy as a day case procedure costs £553; therefore, the GDG concluded that it is highly likely that PIIINP with selective liver biopsy is likely to be the optimal monitoring strategy for patients taking methotrexate. The GDG also considered that the addition of liver function tests to PIIINP is unlikely to add significant costs and may improve the identification of patients needing further investigation.

	In addition to these cost considerations, the GDG considered the risk of serious harm associated with liver biopsy (1-2% risk of injury; 0.01-0.1% risk of mortality). They considered that the potential risk of missing significant liver damage in patients monitored with serial PIIINP to be outweighed by the risks, costs and inconvenience of performing routine liver biopsy on all patients. The GDG discussed the importance of getting these monitoring methods right, as the other treatments available to patients with moderate to severe psoriasis are increasingly toxic and/or costly. Reducing the number of people who are being successfully managed by methotrexate, a very cost-effective treatment, who have a false positive test result and thus move on to more toxic and/or costly strategies could result in a more efficient use of NHS resources.
Quality of evidence	The GDG noted important variables between the studies: • There were differences in whether all participants recruited had a known or suspected diagnosis of liver disease. • Prevalence of fibrosis and cirrhosis varied from 6.9% to 69%. • Unit of analysis: there was variation in whether the study reported one set of paired tests or more than one of each of the tests per patient: o Eight studies used only one index test and one reference standard per person o Three studies included multiple paired index and reference tests per person (Coulson, Lenler, McHenry) o One study included only single paired tests before methotrexate but multiple paired tests after methotrexate (O'Connor) o In two studies it was unclear whether the results were based upon single tests or multiple paired tests per person (Berends, Newman) o One study included more than one index and reference test per patient, and the biopsy was paired with more than one index test (Maurice) • Different scales were used to assess severity of fibrosis on a liver biopsy and it is not possible to map them to a common scale. Study limitations: • Multiple tests per patient could introduce bias by weighting towards those with multiple biopsies (which could be because there was an indication of abnormal liver function or because they had been receiving MTX for longer; but it could also be that those who develop abnormal liver function are taken off MTX which would bias the results in the other direction). However, no clear/consistent impact of different unit of analysis on results • The GDG noted that multiple PIIINP tests are standard, as three or four per year are advised for the purposes of sensitivity. • The GDG also noted that although liver biopsy is used as the gold standard:

	○ It is associated with sampling error and different results can be seen depending on where the sample is taken from in the liver; so if sampling was inadequate the result may misrepresent the true state of the liver ○ Some classification schemes may not detect NAFLD ○ Possible inadequate grading and diverse classification schemes • Experience of the person assessing sample is important and this was not reported in the majority of the studies. • For index tests assessments, there was unclear reporting of methods and different definitions of abnormal were used. • Most studies were retrospective and population sampling methods were unclear (i.e. they may not have used consecutive or random sampling, and difficult to diagnose cases could have been excluded thus introducing bias). The time between test was also unclear in a number of studies. • The GRADE rating for most results is low / very low quality evidence. • Findings for fibrotest and fibroscan are based on a small study and so are insufficient on which to base a recommendation; this is an area for future research. • Ultrasound is very specific but there are only two studies which are very old and may not reflect current ultrasound technology. Further research into ultrasound is desired and the GDG agreed to make a future research recommendation for ultrasound.
Other considerations	• The GDG discussed the psoriatic arthritis (PsA) population and whether PIIINP is useful for this group. Serum procollagen III is cleaved off from collagen when fibrotic tissue is broken down. The PIIINP assay is not liver specific. Therefore the test may be less useful in people with arthritis, as the result could be elevated due to arthritis not the liver. • Fibroscan is currently a research tool and its use is not widespread in dermatology practice (although it is used in hepatology departments). For people with a BMI >30, a special probe is needed for fibroscan, which costs and additional £30K. • The data on LFTs is counter-intuitive, and the GDG discussed whether some of the tests should not be used. The GDG only looked at the endpoints of fibrosis and cirrhosis. LFTs detect other issues including idiosyncratic hepatotoxic reaction to methotrexate, non-alcoholic fatty liver disease and excessive alcohol consumption. Therefore the GDG agreed not to make a 'do not use' recommendation for any of the LFTs. • The GDG wished to capture people in the recommendations who have serial abnormal test results over time due to development of fibrosis. Acute hepatotoxic reaction to methotrexate would be detected by an acute rapidly rising abnormality of LFT. The GDG agreed to recommend that people with psoriasis taking methotrexate should be assessed for fibrosis or cirrhosis using PIIINP and LFTs. • People with serial abnormal results should be referred for specialist opinion to assess risk and benefits of continuing methotrexate.

	Specialist opinion could be sought from a hepatalogist or gastroenterologist in view of the potential lack of availability of hepatologists in some areas. • The GDG debated whether methotrexate should be stopped while waiting for a referral. Stopping treatment for three months in someone with severe disease and /or with arthritis could have devastating consequences. There is not an urgent need for expedient referrals in this group; the group in which urgent referral would be needed is people with bone marrow failure. Therefore no recommendation was made about stopping methotrexate while waiting for specialist appointment. • People with psoriasis have comorbidities that may predispose them to abnormal liver function, such as obesity and diabetes. This does not preclude the use of methotrexate, but it is extremely important to test liver function prior to therapy and monitor during therapy in case fibrosis develops in this high risk population. • Methotrexate is known to be a hepatotoxic drug in the short term (at least) and certain factors especially prevalent in people with severe psoriasis (diabetes, obesity, alcohol related morbidity) are also associated with liver dysfunction; the GDG therefore agreed that a recommendation highlighting that when using methotrexate, any clinical factors that might impact on liver function should be taken into account, that abnormalities that develop need to be considered in this context and advice given on safe alcohol intake.

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13 Systemic (Biological therapy)

Over the last 5 years or so, biological therapies have been introduced into the treatment paradigm for psoriasis (and also psoriatic arthritis) and have revolutionised the management of severe disease, with improved outcomes and reduced length of hospital inpatient stays. Three TNF antagonists (adalimumab, etanercept and infliximab), and the IL12/23 monoclonal antibody are licensed for use in moderate and severe psoriasis.

All four agents are approved for use by NICE in people who have failed to respond to systemic non-biological therapies including ciclosporin, methotrexate and PUVA or the person is intolerant to, or has a contraindication to, these treatments, subject to certain disease severity criteria (which for etanercept, adalimumab and ustekinumab, are a PASI >10 and a DLQI >10 [severe disease] [7,8,10]., and for infliximab, a PASI>20 and a DLQI >18 [very severe disease] [406]).

These drugs are extremely effective and generally well tolerated in the majority of people but have high acquisition costs. Explicit guidance from NICE on indications for use and continued use has been fundamental to ensuring equality of access to biological therapy for people with severe or very severe disease. In a minority of people, treatment is complicated by a poor response to treatment that may be either a primary non response or, more commonly, gradual attrition of response with time. These individuals by definition have difficult disease where standard interventions cannot be used. Clinical experience in psoriasis, and also in other inflammatory conditions such as Crohn's disease and rheumatoid and psoriatic arthritis, suggest that a second and subsequent biological drug may also be effective. Some studies have suggested that response rates to a second biological drug may be lower than that to the first, and also that even in those who do respond, the duration of response may be shortened. The experience of the GDG is that patients who fail to respond to a biological therapy are likely to have even more severe psoriasis and even greater health service use than the average patient eligible for these drugs.

In view of these issues, the GDG agreed to ask the following review question: in people with psoriasis eligible to receive biological therapy, if the first biological drug fails, which is the next effective, safe and cost effective strategy?

13.1 Methodological introduction

A literature search was conducted for randomised controlled trials (RCTs), systematic reviews or comparative observational data that addressed the efficacy and safety of switching to etanercept, infliximab, adalimumab or ustekinumab after previously receiving a first biological drug in people with psoriasis. No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. The population was limited to adults with chronic plaque psoriasis because biological treatments are currently only licensed for use among this subset of people with psoriasis; indirect populations were excluded.

The outcomes considered were:

- PASI75
- PASI50
- Change in PASI (mean improvement) or final PASI as a surrogate outcome
- Clear or nearly clear (minimal residual activity[MRA]/PASI>90/0 or 1 on PGA)
- Time-to-relapse (loss of PASI50)
- Change in DLQI
- Severe adverse events
- Withdrawal due to toxicity

- Withdrawal due to lack of efficacy

Comparative data were accepted for inclusion if they were able to demonstrate whether or not there was an independent treatment effect for first and second biological drugs. This included:

- Randomised comparisons of biological drug vs placebo or other biological drug, with subgroup data for those who had and had not previously received biological therapy
- Non-randomised comparisons of treatment response to biological drugs stratified by previous exposure to biological drugs
- Studies that specified that people had either failed or received a previous biological drug

Eight studies were found that addressed the question and were included in the review (see Table 173).

- Three case series with data stratified for previous exposure to biological therapies[407-409]
- Two sub-analyses of non-randomised data from RCTs[410,411]
- Two RCTs: one comparing response rate between placebo and infliximab with subgroup analysis for prior use of biological therapy[412] and one crossover trial comparing response to ustekinumab in the first phase of the trial with response to ustekinumab in patients who had failed to respond to etanercept[413]
- One cohort study[414]

Additional data were made available through a call for evidence and from this the following were also included in the review:

- Two case series with data stratified for previous exposure to biological therapies[415,416]
- One subgroup analysis of an included study[414], giving data for the numbers of primary and secondary non-responders (i.e., the number who never responded or responded initially but lost response, respectively)
- Unpublished randomised and non-randomised data from three published RCTs[410,413,417], two of which were already included in the review[410,413]. The data available were response rates for placebo and ustekinumab[418,419] or ustekinumab and etanercept[420], with subgroup analysis for prior use of biological therapy

Of the included studies there was variation in the definition of prior exposure to biological therapy:

- Four specified that people had failed a previous biological drug[407,408,413,414]
  - One of these studies[421] gave subgroup information for those who never responded or lost an initial response)
- Seven only stated whether or not they had received a previous biological drug[409,411,412,415,418-420]
  - One of these studies[411] also presented stratified data regarding the reason for discontinuation.
- Two studies included data on both those who had failed and those who had just received a previous biological drug[410,416].

When interpreting the results of observational studies summarised as relative risk or mean difference it is necessary to apply particular caution if there has been no explicit balancing or adjusting for confounders within the study. This is because the differences between intervention and comparison groups may be due to factors other than the experimental variables themselves. Additionally, the results of observational studies have not been pooled owing to inconsistencies in design and comparison, as well as the potential confounders. As the effects reported may differ from the true underling effects in ways that are systematically different from chance, combining such studies will increase the precision of an inaccurate result and may lead to inappropriate conclusions.

Only one of the observational studies included in the review adequately adjusted for confounders (including treatment group, number of prior systemic non-biological therapies (>3, ≤3), age, duration

of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline) in the analysis[411].

Table 173: Summary of study characteristics

Study	Study design	Concomitant PsA (%)	Comparison	Prior biological therapy (proportion of those previously exposed receiving different interventions)	Treatment
CASSANO 2008	Stratified case series (prospective)	100.0%	Received previous biological therapy vs no previous biological therapy	Infliximab and/or etanercept in all but 2 cases (who had used efalizumab[b])	Adalimumab (subcutaneously) 40 mg every other week
GRIFFITHS 2010	Randomised controlled trial	27.9%	Crossover to ustekinumab after etanercept failure vs ustekinumab during the first phase of the trial	Included alefacept, efalizumab, infliximab, and adalimumab (proportions unclear)	Ustekinumab: 90 mg at weeks 0 and 4 (or weeks 16 and 20 if crossed over from etanercept) Etanercept: 50 mg twice weekly Note: in the group who received ustekinumab in the first phase of the trial 10.4% had also received a previous biological therapy
JANSSENCILAG2011	Randomised controlled trial	27.9%	Etanercept vs ustekinumab (with subgroups for ever and never used biological therapy within each group)	Included etanercept, alefacept, efalizumab, infliximab, and adalimumab (proportions unclear)	Ustekinumab[(a)]: 45 or 90 mg at weeks 0 and 4 Etanercept: 50 mg twice weekly *Note: only those with PASI75 response at week 28 and who continued on active treatment up to week 52 were analysed (second randomisation at week 40 for withdrawal phase: those randomised to placebo not included in analysis)*
JANSSENCILAG2011A	Randomised controlled trial	33.7%	Ustekinumab vs placebo (with subgroups for ever and never used biological therapy within each group)	Included alefacept, efalizumab, infliximab, and adalimumab (proportions unclear)	Ustekinumab[(a)] (subcutaneously): 45 or 90 mg at weeks 0 and 4 and then every 12 weeks
JANSSENCILAG2011B	Randomised controlled trial	24.9%	Ustekinumab vs placebo (with subgroups for ever and never used biological therapy within each group)	Included etanercept, alefacept, efalizumab, infliximab, and adalimumab (proportions unclear)	Ustekinumab[(a)] (subcutaneously): 40 or 90 mg at weeks 0 and 4 and then every 12 weeks *Note: only those with PASI75 response at week 28 and who continued on the same dose of ustekinumab up to week 52 were analysed (second randomisation at week 28 for dose intensification*

Study	Study design	Concomitant PsA (%)	Comparison	Prior biological therapy (proportion of those previously exposed receiving different interventions)	Treatment
					phase: those with increased frequency of administration not included in analysis)
LAWS 2011	Stratified case series (retrospective)	34.9%	Received previous biological therapy vs no previous biological therapy	Included etanercept, efalizumab, infliximab, and adalimumab (proportions unclear)	Ustekinumab, induction therapy at weeks 0 and 4 and then every 12 weeks. Weight dependent dosing: ≤100kg given 45mg >100kg given 90mg ***Note**: Overlap therapy (medication co-prescribed during induction of ustekinumab therapy) and rescue therapy (additional medication required following the induction phase) were permitted.*
MAZZOTTA 2009	Stratified case series (prospective)	47.0%	Failed previous biological therapy vs no previous biological therapy	Infliximab (93%) and efalizumab (7%)	Etanercept (self-administered subcutaneously) 0-12 weeks: 50 mg twice weekly 13-24 weeks: dose reduced to 25 mg twice weekly
MENTER 2007	Randomised controlled trial	27.5%	Infliximab vs placebo; with subgroup data for those who had received previous biological therapy vs no previous biological therapy	Unclear	Placebo vs infliximab (intravenous infusion): 3 or 5 mg/kg at weeks 0, 2 and 6 ***Note:** data from two dose groups pooled for outcome of interest*
ORTONNE 2011	Stratified case series within RCT (prospective)	28.1%	Received previous TNF antagonist vs no previous TNF antagonist	Etanercept (36.9%), infliximab (16.7%) or certolizumab (3.2%)	Adalimumab (subcutaneously): 80 mg at wk 0, then 40 mg every other week to week 15 ***Note:** 50% of patients self-administered concomitant topical calcipotriol 52.2 µg/g plus betamethasone dipropionate 0.64 mg/g once daily (application not to exceed 30% BSA or 100g per week)*
PAPP 2008	Stratified case series within RCT (prospective)	24.9%	Failed or received previous biological therapy vs no previous biological therapy	Included etanercept, alefacept, efalizumab, infliximab, and adalimumab (proportions unclear)	Ustekinumab (subcutaneously): 40 or 90 mg at weeks 0 and 4 and then every 12 weeks

Study	Study design	Concomitant PsA (%)	Comparison	Prior biological therapy (proportion of those previously exposed receiving different interventions)	Treatment
PAPP 2012	Stratified case series (prospective)	36.9%	i. No prior exposure to biological therapy ii. Prior exposure to biological therapy iii. Prior exposure to etanercept or infliximab iv. Failed any prior biological therapy v. Failed prior etanercept or infliximab vi. Failed 1 prior biological drug vii. Failed ≥2 prior biological drugs	Etanercept (32.1%), alefacept (23.1%), ustekinumab (23.1%), efalizumab (21.8%), infliximab (20.5%), and other (17.9%)	Adalimumab, self-administered; loading dose of 80 mg adalimumab subcutaneously at baseline, followed by 40 mg subcutaneously every other week starting at week 1 ***Note**: Doses and regimens of concomitant medications and therapies for the treatment of psoriasis that the patient was receiving at baseline (topical, systemic non-biological or phototherapy) could be tapered off, stopped or remain stable from baseline until week 16. The initiation of new topical, systemic non-biological or light therapies (with the exception of topical therapies for the palms, soles of feet, axilla and groin), or an increase in the dosing regimen of existing therapies could not occur before the week 16 visit.*
STROBER 2011	Cohort study (prospective)	46.7%	Failed previous etanercept, methotrexate or NBUVB	Etanercept	Adalimumab 80 mg at week 0 and 40 mg every other week beginning at week 1 through to week 15 Self-administered using pre-filled auto-injection device
STROBER 2012	Cohort study (prospective)	46.7%	Failed previous etanercept, methotrexate or NBUVB (plus subgroups for primary and secondary non-responders)	Etanercept	Adalimumab 80 mg at week 0 and 40 mg every other week beginning at week 1 through to week 15 Self-administered using pre-filled auto-injection device
VAN 2008H	Stratified case series (retrospective)	Unclear	Failed previous biological therapy vs no previous biological therapy	Etanercept (38.5%), infliximab (74.4%), and efalizumab (15.4%)	Adalimumab, 40 mg weekly After 12 weeks patients "clear" or "almost clear" by PGA had their doses decreased to once every 2 weeks, while the remainder continued weekly dosing for another 3 months. Patients were reassessed at 3- to 6-month intervals,

Study	Study design	Concomitant PsA (%)	Comparison	Prior biological therapy (proportion of those previously exposed receiving different interventions)	Treatment
					and dosing frequency decreased if appropriate.

(a) From the call for evidence, outcome data were available for the subset of people who had received the licensed, weight-based dosing. However, the full sample was analysed in order to maximise power and because any under- and over-dosing and hence potential under- and over-estimations of efficacy should balance out.

(b) Efalizumab has been withdrawn by the European Medicines Agency due to progressive leukoencephalopathy

13.2 Previous biological therapy vs. no previous biological therapy

Etanercept in those with and without prior exposure to biological therapy

13.2.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Etanercept in those with prior exposure to biological therapy	No previous biological therapy	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90; week 12)											
1 ACCEPT unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	serious[b]	very serious[c]	none	4/27 (14.8%)	76/319 (23.8%)	RR 0.62 (0.25 to 1.57)	91 fewer per 1000 (from 179 fewer to 136 more)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 12)											
1 ACCEPT unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	serious[b]	serious[d]	none	10/27 (37%)	159/319 (49.8%)	RR 0.74 (0.45 to 1.23)	130 fewer per 1000 (from 274 fewer to 115 more)	⊕OOO VERY LOW
PASI75 (week 12)											

1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[f]	serious[d]	none	19/56 (33.9%)	79/178 (44.4%)	RR 0.76 (0.51 to 1.14)	107 fewer per 1000 (from 217 fewer to 62 more)	⊕OOO VERY LOW
PASI75 (week 12)											
1 ACCEPT unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	serious[b]	serious[d]	none	10/27 (37%)	186/319 (58.3%)	RR 0.64 (0.39 to 1.05)	210 fewer per 1000 (from 356 fewer to 29 more)	⊕OOO VERY LOW
PASI75 (week 24) - subgroup with psoriasis affecting the skin only											
1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[f]	serious[d]	none	17/26 (65.4%)	74/98 (75.5%)	RR 0.87 (0.64 to 1.17)	98 fewer per 1000 (from 272 fewer to 128 more)	⊕OOO VERY LOW
PASI75 (week 24) - subgroup with psoriasis and concomitant psoriatic arthritis											
1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[f]	no serious imprecision	none	9/30 (30%)	59/80 (73.8%)	RR 0.41 (0.23 to 0.71)	435 fewer per 1000 (from 214 fewer to 568 fewer)	⊕OOO VERY LOW
PASI50 (week 12)											
1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[f]	serious[d]	none	36/56 (64.3%)	132/178 (74.2%)	RR 0.88 (0.71 to 1.09)	89 fewer per 1000 (from 215 fewer to 67 more)	⊕OOO VERY LOW
PASI50 (week 12)											
1 ACCEPT unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	serious[b]	serious[d]	none	20/27 (74.1%)	265/319 (83.1%)	RR 0.89 (0.71 to 1.12)	91 fewer per 1000 (from 241 fewer to 100 more)	⊕OOO VERY LOW
PASI50 (week 24) - subgroup with psoriasis affecting the skin only											
1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[f]	serious[d]	none	18/26 (69.2%)	88/98 (89.8%)	RR 0.77 (0.59 to 1)	207 fewer per 1000 (from 368 fewer to 0 more)	⊕OOO VERY LOW
PASI50 (week 24) - subgroup with psoriasis and concomitant psoriatic arthritis											
1	observational	very	no serious	serious[f]	no serious	none	14/30	74/80	RR 0.5 (0.34	463 fewer per 1000	⊕OOO

Mazzotta 2009	studies	serious[e]	inconsistency		imprecision		(46.7%)	(92.5%)	to 0.74)	(from 240 fewer to 610 fewer)	VERY LOW
% improvement in PASI (week 12) (better indicated by higher values)											
1 ACCEPT unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	serious[b]	serious[d]	none	27	311	-	MD 7.04 lower (17.22 lower to 3.14 higher)	⊕OOO VERY LOW
Final PASI (week 12) (better indicated by lower values)											
1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[7]	no serious imprecision	none	56	178	-	MD 0.18 higher (0.81 lower to 1.17 higher)	⊕OOO VERY LOW
Final PASI (week 24 – dose reduced for the last 12 weeks) (better indicated by lower values)											
1 Mazzotta 2009	observational studies	very serious[e]	no serious inconsistency	serious[g]	no serious imprecision	none	56	178	-	MD 1.64 higher (0.69 higher to 2.59 higher)	⊕OOO VERY LOW

(a) Similar baseline characteristics in those with and without prior exposure to biological therapy; but slightly longer disease duration (1.1 years), higher proportion male (by 7.6%) and lower proportion with marked to severe disease (by 6.3%) in those with prior exposure to biological therapy. Acceptable dropout rate but unclear if different for those with and without prior exposure to biological therapy

(b) High dose of etanercept (50 mg twice weekly). Prior biological drugs included alefacept and efalizumab (proportions unclear)

(c) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect

(d) Confidence interval ranges from clinically important effect to no effect

(e) Failure to adequately control for confounding (no matching for prognostic factors or adjustment in statistical analyses); PsA and psoriasis cohorts not matched for age, previous interventions or skin disease severity at baseline (PASI)

(f) Unlicensed dosing for first 12 weeks (50 mg twice weekly). 47% PsA and 4/27 (14.8%) in psoriasis cohort switched from efalizumab

(g) Surrogate outcome for change in PASI. Unlicensed dosing for first 12 weeks (50 mg twice weekly). Also note: 47% PsA and 4/27 (14.8%) in psoriasis cohort switched from efalizumab

13.2.11 Evidence statements

In people with psoriasis being treated with etanercept, those with no prior exposure to biological therapy had a statistically significantly better result than those with previous biological therapy exposure for:

- PASI75 at 24 weeks (concomitant PsA subgroup) [1 study; 110 participants; very low quality evidence][407]
- PASI50 at 24 weeks (concomitant PsA subgroup) [1 study; 110 participants; very low quality evidence][407]
- Final PASI at 24 weeks [1 study; 234 participants; very low quality evidence][407]

Even though cases where those with no prior exposure to biological therapy had a statistically significantly better result, those who had previously received a biological therapy still had substantial response rates (32.1% PASI75; 46.7% PASI50).

In people with psoriasis being treated with etanercept, there was no statistically significant difference between those with and without prior exposure to biological therapy for:

- Clear/nearly clear (PASI90 or PGA) at 12 weeks [1 study; 346 participants; very low quality evidence][420]
- PASI75 at 12 weeks [2 studies; 580 participants; very low quality evidence][407,420]
- PASI75 at 24 weeks (psoriasis only subgroup) [1 study; 124 participants; very low quality evidence][407]
- PASI50 at 12 weeks [2 studies; 580 participants; very low quality evidence][407,420]
- PASI50 at 24 weeks (psoriasis only subgroup) [1 study; 124 participants; very low quality evidence][407]
- % improvement in PASI at 12 weeks [1 study; 338 participants; very low quality evidence][420]
- Final PASI at 12 weeks [1 study; 234 participants; very low quality evidence][407]

13.2.122 Subgroup analyses and heterogeneity

- One study[407] presented the response rates on etanercept among those with and without exposure to a previous biological drug separately for those with and without concomitant psoriatic arthritis.

There were no significant subgroup differences on the outcomes of:

- PASI75 at 12 weeks
- PASI50 at 12 weeks
- Final PASI at 12 or 24 weeks

However, there were significant subgroup differences on the outcomes of:

- PASI75 at 24 weeks (the PsA subgroup more strongly favoured those with no previous exposure to biological therapy)
- PASI50 at 24 weeks (the PsA subgroup more strongly favoured those with no previous exposure to biological therapy)

Differences at baseline between those with and without concomitant PsA were that those with PsA were older, had a different pattern of exposure to previous systemic non-biological agents and less severe cutaneous disease. It is not possible to determine whether the heterogeneity was caused just by the difference in joint involvement, but it is noteworthy that it only occurred at the 24 week assessment point after the dose of etanercept had been reduced.

1 Adalimumab in those with and without prior exposure to biological therapy

13.22 Evidence profile

3

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adalimumab in those with previous exposure to biological therapy	No previous exposure to biological therapy	Relative (95% CI)	Absolute	
Clear/nearly clear (sustained response: 12 months) - any previous biological drug											
1 Van 2008	observational studies	very serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	31/39 (79.5%)	7/10 (70%)	RR 1.14 (0.73 to 1.76)	98 more per 1000 (from 189 fewer to 532 more)	⊕OOO VERY LOW
Clear/nearly clear (sustained response: 12 months) - previous TNF antagonist											
1 Van 2008	observational studies	very serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	29/37 (78.4%)	7/10 (70%)	RR 1.12 (0.72 to 1.74)	84 more per 1000 (from 196 fewer to 518 more)	⊕OOO VERY LOW
PASI75 (week 12)											
1 Cassano 2008	observational studies	very serious[a]	no serious inconsistency	serious[d]	serious[e]	none	56	88	Among responders (at least PASI50) the likelihood of achieving PASI75 was higher in patients who were naïve to biological therapy (47.5%) compared to those who had been treated with biological therapy in the past (26%); p=0.03		⊕OOO VERY LOW
PASI75 (week 16) - Any biological therapy exposure vs none (follow-up 16 weeks)											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	no serious imprecision	none	51/78 (65.4%)	93/125 (74.4%)	RR 0.88 (0.73 to 1.06)	89 fewer per 1000 (from 201 fewer to 45 more)	⊕OOO VERY LOW
PASI75 (week 16) - Any anti-TNF exposure vs no biological therapy exposure (follow-up 16 weeks)											

1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	no serious imprecision	none	27/37 (73%)	93/125 (74.4%)	RR 0.98 (0.79 to 1.22)	15 fewer per 1000 (from 156 fewer to 164 more)	⊕OOO VERY LOW
PASI75 (week 16) - Failed prior biological drug vs no biological exposure (follow-up 16 weeks)											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	24/40 (60%)	93/125 (74.4%)	RR 0.81 (0.61 to 1.06)	141 fewer per 1000 (from 290 fewer to 45 more)	⊕OOO VERY LOW
PASI75 (week 16) - Failed prior anti-TNF vs no biological exposure (follow-up 16 weeks)											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	very serious[c]	none	12/17 (70.6%)	93/125 (74.4%)	RR 0.95 (0.69 to 1.31)	37 fewer per 1000 (from 231 fewer to 231 more)	⊕OOO VERY LOW
PASI75 (week 16) - Failed at least 2 prior biological drugs vs no biological exposure (follow-up 16 weeks)											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	17/25 (68%)	93/125 (74.4%)	RR 0.91 (0.69 to 1.22)	67 fewer per 1000 (from 231 fewer to 164 more)	⊕OOO VERY LOW
PASI75 (week 24) - Any biological exposure vs none											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	48/78 (61.5%)	92/125 (73.6%)	RR 0.84 (0.68 to 1.03)	118 fewer per 1000 (from 236 fewer to 22 more)	⊕OOO VERY LOW
PASI75 (week 24) - Any anti-TNF exposure vs no biological exposure											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	28/37 (75.7%)	92/125 (73.6%)	RR 1.03 (0.83 to 1.27)	22 more per 1000 (from 125 fewer to 199 more)	⊕OOO VERY LOW
PASI75 (week 24) - Failed prior biological drug vs no biological exposure											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	24/40 (60%)	92/125 (73.6%)	RR 0.82 (0.62 to 1.07)	132 fewer per 1000 (from 280 fewer to 52 more)	⊕OOO VERY LOW
PASI75 (week 24) - Failed prior anti-TNF vs no biological exposure											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	10/17 (58.8%)	92/125 (73.6%)	RR 0.8 (0.53 to 1.21)	147 fewer per 1000 (from 346 fewer to 155 more)	⊕OOO VERY LOW

PASI75 (week 24) - Failed at least 2 prior biological drugs vs no biological exposure											
1 Papp 2012	observational studies	very serious[a]	no serious inconsistency	serious[f]	serious[g]	none	14/25 (56%)	92/125 (73.6%)	RR 0.76 (0.53 to 1.09)	177 fewer per 1000 (from 346 fewer to 66 more)	⊕OOO VERY LOW
PASI50 (week 12)											
1 Cassano 2008	observational studies	very serious[a]	no serious inconsistency	serious[d]	serious[e]	none	56	88	No consistent or significant differences in the PASI50 response rates between patients previously treated with only traditional non-biological systemics and those treated with biological drugs (p>0.05)		⊕OOO VERY LOW

(a) Failure to adequately control for confounding (no matching for prognostic factors or adjustment in statistical analyses)
(b) Unlicensed dosing (once weekly). Also, unclear how many had concomitant PsA and a minority had used efalizumab as a previous biological drug
(c) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect
(d) 100% concomitant PsA; 3.6% of those receiving previous biological drugs had used efalizumab
(e) Absolute numbers not provided
(f) 67.5% had one or more concomitant therapies: corticosteroids (40.4%; 38.2% topical and 2.2% systemic), vitamin D and analogues (17.7%), methotrexate (11.3%), phototherapy (4.9%) and high proportion had received prior biological drugs not licensed for psoriasis.
(g) Confidence interval ranges from clinically important effect to no effect

13.2.3 Evidence statements

In people with psoriasis being treated with adalimumab, there was no statistically significant difference between those with and without prior exposure (including all definitions of this comparison) to biological therapy for:

- Clear/nearly clear at 12 months [1 study; 49 participants; very low quality evidence][408]
- PASI75 at 16 weeks [1 study; 142 to 203 participants; very low quality evidence][415,416]
- PASI75 at 24 weeks [1 study; 142 to 203 participants; very low quality evidence][416]

Evidence statements for Cassano et al 2008 where no original analysis could be performed comparing those with and without prior exposure to biological therapy (note that this study stated that people had been treated with previous biologics; the reason for discontinuation could have been unsatisfactory clinical response/loss of efficacy (<PASI50), adverse events that could compromise treatment continuation or poor compliance):

- There was no statistically significant difference between those with and without prior exposure to biological therapy for PASI50 at 12 weeks on adalimumab [1 study; 144 participants; very low quality evidence][409]
- There was a statistically significantly higher likelihood of achieving PASI75 among those who achieved at least PASI50 at 12 weeks on adalimumab for those without prior exposure to biological therapy compared with those with prior exposure [1 study; 144 participants; very low quality evidence][409]. This study stated that people had been treated with previous biologics; the reason for discontinuation could have been unsatisfactory clinical response/loss of efficacy (<PASI50), adverse events that could compromise treatment continuation or poor compliance.

13.2.3.71 Subgroup analyses and heterogeneity

- One study[408] presented the numbers clear or nearly clear for those with and without exposure to both any previous biological therapy and any previous TNF antagonist before switching to adalimumab. There was no inconsistency between these two subgroups.
- One study[416] presented the outcome of PASI75 for patients naïve to biological therapy compared with those who had any previous exposure to biological therapy, any previous anti-TNF exposure, prior failure of any biological drug, failure of any anti-TNF agent and failure of at least 2 prior biological drugs. All comparisons showed no significant difference and there was no inconsistency between any of the subgroup comparisons.

Infliximab in those with and without prior exposure to biological therapy

13.2.44 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab in those with previous biological therapy	No previous biological therapy	Relative (95% CI)	Absolute	
PASI 75 (week 10) (follow-up 10 weeks)											
1 Menter 2007	observational studies	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	68/94 (72.3%)	389/533 (73%)	RR 0.99 (0.87 to 1.13)	7 fewer per 1000 (from 95 fewer to 95 more)	⊕OOO VERY LOW

(a) Failure to adequately control for confounding (no matching for prognostic factors or adjustment in statistical analyses); unclear if differential drop-out rate
(b) Follow-up only 10 weeks (BNF suggests discontinuation if no response after 14 weeks)

13.215 Evidence statements

In people with psoriasis being treated with infliximab, there was no statistically significant difference between those with and without prior exposure to biological therapy for:

- PASI75 at 10 weeks [1 study; 627 participants; very low quality evidence][412]

Ustekinumab in those with and without prior exposure to biological therapy

13.216 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ustekinumab in those with previous biological therapy	No previous biological therapy	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90; week 12)											
1 ACCEPT – unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	10/36 (27.8%)	221/519 (42.6%)	RR 0.65 (0.38 to 1.12)	149 fewer per 1000 (from 264 fewer to 51 more)	⊕OOO VERY LOW
Clear/nearly clear (PASI90; week 12)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	75/212 (35.4%)	125/299 (41.8%)	RR 0.85 (0.68 to 1.06)	63 fewer per 1000 (from 134 fewer to 25 more)	⊕OOO VERY LOW
Clear/nearly clear (PASI90; week 12)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	94/250 (37.6%)	288/570 (50.5%)	RR 0.74 (0.62 to 0.89)	131 fewer per 1000 (from 56 fewer to 192 fewer)	⊕OOO VERY LOW
Clear/nearly clear (PASI90; week 24)											

1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	114/207 (55.1%)	182/290 (62.8%)	RR 0.88 (0.75 to 1.02)	75 fewer per 1000 (from 157 fewer to 13 more)	⊕OOO VERY LOW
Clear/nearly clear (PASI90; week 24)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	113/242 (46.7%)	329/558 (59%)	RR 0.79 (0.68 to 0.92)	124 fewer per 1000 (from 47 fewer to 189 fewer)	⊕OOO VERY LOW
Clear/nearly clear (PASI90; week 52)											
1 PHOENIX1 – unpublished data	observational studies	serious[f]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	39/59 (66.1%)	66/103 (64.1%)	RR 1.03 (0.82 to 1.3)	19 more per 1000 (from 115 fewer to 192 more)	⊕OOO VERY LOW
Clear/nearly clear (PASI90; week 52)											
1 PHOENIX2 – unpublished data	observational studies	serious[g]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	86/148 (58.1%)	276/389 (71%)	RR 0.82 (0.7 to 0.95)	128 fewer per 1000 (from 35 fewer to 213 fewer)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 12)											
1 ACCEPT – unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	19/36 (52.8%)	362/519 (69.7%)	RR 0.76 (0.55 to 1.04)	167 fewer per 1000 (from 314 fewer to 28 more)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 12)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	122/212 (57.5%)	190/299 (63.5%)	RR 0.91 (0.78 to 1.05)	57 fewer per 1000 (from 140 fewer to 32 more)	⊕OOO VERY LOW

Clear/nearly clear (PGA; week 12)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	162/250 (64.8%)	418/570 (73.3%)	RR 0.88 (0.8 to 0.98)	88 fewer per 1000 (from 15 fewer to 147 fewer)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 24)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	137/207 (66.2%)	213/290 (73.4%)	RR 0.9 (0.8 to 1.02)	73 fewer per 1000 (from 147 fewer to 15 more)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 24)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	159/242 (65.7%)	419/558 (75.1%)	RR 0.87 (0.79 to 0.97)	98 fewer per 1000 (from 23 fewer to 158 fewer)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 52)											
1 PHOENIX1 – unpublished data	observational studies	serious[f]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	43/59 (72.9%)	72/103 (69.9%)	RR 1.04 (0.85 to 1.27)	28 more per 1000 (from 105 fewer to 189 more)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 52)											
1 PHOENIX2 – unpublished data	observational studies	serious[g]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	98/148 (66.2%)	291/389 (74.8%)	RR 0.89 (0.78 to 1.01)	82 fewer per 1000 (from 165 fewer to 7 more)	⊕OOO VERY LOW
PASI75 (week 12)											
1 ACCEPT – unpublish	observational studies	no serious risk of bias[a]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	20/36 (55.6%)	377/519 (72.6%)	RR 0.76 (0.57 to 1.03)	174 fewer per 1000 (from 312 fewer to 22 more)	⊕OOO VERY LOW

ed data											
PASI75 (week 12)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	128/212 (60.4%)	213/299 (71.2%)	RR 0.85 (0.74 to 0.97)	107 fewer per 1000 (from 21 fewer to 185 fewer)	⊕OOO VERY LOW
PASI75 (week 12)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	158/250 (63.2%)	426/570 (74.7%)	RR 0.85 (0.76 to 0.94)	112 fewer per 1000 (from 45 fewer to 179 fewer)	⊕OOO VERY LOW
PASI75 (week 16) - Any biological exposure vs none (follow-up 16 weeks)											
1 Laws 2011	observational studies	very serious[h]	no serious inconsistency	serious[i]	serious[c]	none	64/106 (60.4%)	16/21 (76.2%)	RR 0.79 (0.6 to 1.05)	160 fewer per 1000 (from 305 fewer to 38 more)	⊕OOO VERY LOW
PASI75 (week 16) - None or one prior biological drug vs 2-4 prior biological drugs (follow-up 16 weeks)											
1 Laws 2011	observational studies	very serious[h]	no serious inconsistency	serious[i]	serious[c]	none	45/79 (57%)	35/48 (72.9%)	RR 0.78 (0.6 to 1.01)	160 fewer per 1000 (from 292 fewer to 7 more)	⊕OOO VERY LOW
PASI75 (week 24)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	155/207 (74.9%)	245/290 (84.5%)	RR 0.89 (0.81 to 0.97)	93 fewer per 1000 (from 25 fewer to 161 fewer)	⊕OOO VERY LOW
PASI75 (week 24)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	181/242 (74.8%)	446/558 (79.9%)	RR 0.94 (0.86 to 1.02)	48 fewer per 1000 (from 112 fewer to 16 more)	⊕OOO VERY LOW
PASI75 (week 28)											

1 Papp 2008	observational studies	serious[e]	no serious inconsistency[j]	no serious indirectness[b]	no serious imprecision[k]	none	209/307 (68.1%)	380/513 (74.1%)	RR 0.92 (0.84 to 1.01)	59 fewer per 1000 (from 119 fewer to 7 more)	⊕OOO VERY LOW
PASI75 (week 52)											
1 PHOENIX1 – unpublished data	observational studies	serious[f]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	51/59 (86.4%)	93/103 (90.3%)	RR 0.96 (0.85 to 1.08)	36 fewer per 1000 (from 135 fewer to 72 more)	⊕OOO VERY LOW
PASI75 (week 52)											
1 PHOENIX2 – unpublished data	observational studies	serious[g]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	127/148 (85.8%)	360/389 (92.5%)	RR 0.93 (0.86 to 1)	65 fewer per 1000 (from 130 fewer to 0 more)	⊕OOO VERY LOW
PASI50 (week 12)											
1 ACCEPT – unpublished data	observational studies	no serious risk of bias[a]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	28/36 (77.8%)	473/519 (91.1%)	RR 0.85 (0.72 to 1.02)	137 fewer per 1000 (from 255 fewer to 18 more)	⊕OOO VERY LOW
PASI50 (week 12)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	171/212 (80.7%)	262/299 (87.6%)	RR 0.92 (0.85 to 1)	70 fewer per 1000 (from 131 fewer to 0 more)	⊕OOO VERY LOW
PASI50 (week 12)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	213/250 (85.2%)	496/570 (87%)	RR 0.98 (0.92 to 1.04)	17 fewer per 1000 (from 70 fewer to 35 more)	⊕OOO VERY LOW
PASI50 (week 24)											

1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	186/207 (89.9%)	275/290 (94.8%)	RR 0.95 (0.9 to 1)	47 fewer per 1000 (from 95 fewer to 0 more)	⊕OOO VERY LOW
PASI50 (week 24)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	225/242 (93%)	517/558 (92.7%)	RR 1 (0.96 to 1.05)	0 fewer per 1000 (from 37 fewer to 46 more)	⊕OOO VERY LOW
PASI50 (week 52)											
1 PHOENIX1 – unpublished data	observational studies	serious[f]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	57/59 (96.6%)	101/103 (98.1%)	RR 0.99 (0.93 to 1.04)	10 fewer per 1000 (from 69 fewer to 39 more)	⊕OOO VERY LOW
PASI50 (week 52)											
1 PHOENIX2 – unpublished data	observational studies	serious[g]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	146/148 (98.6%)	386/389 (99.2%)	RR 0.99 (0.97 to 1.02)	10 fewer per 1000 (from 30 fewer to 20 more)	⊕OOO VERY LOW
% improvement in PASI (week 12) (better indicated by higher values)											
1 ACCEPT – unpublished data	observational studies	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	35	508	-	MD 13.75 lower (24.4 to 3.1 lower)	⊕⊕OO LOW
% improvement in PASI (week 12) (better indicated by higher values)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	208	298	-	MD 5.55 lower (10.17 to 0.93 lower)	⊕OOO VERY LOW

% improvement in PASI (week 12) (better indicated by higher values)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	248	564	-	MD 4.19 lower (7.76 to 0.62 lower)	⊕OOO VERY LOW
% improvement in PASI (week 24) (better indicated by higher values)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	207	290	-	MD 4.37 lower (8.27 to 0.47 lower)	⊕OOO VERY LOW
% improvement in PASI (week 24) (better indicated by higher values)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	123	283	-	MD 2.69 lower (7.25 lower to 1.87 higher)	⊕OOO VERY LOW
% improvement in PASI (week 52) (better indicated by higher values)											
1 PHOENIX1 – unpublished data	observational studies	serious[f]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	59	103	-	MD 0.7 lower (5.4 lower to 4 higher)	⊕OOO VERY LOW
% improvement in PASI (week 52) (better indicated by higher values)											
1 PHOENIX2 – unpublished data	observational studies	serious[g]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	148	389	-	MD 3.74 lower (6.39 to 1.09 lower)	⊕OOO VERY LOW
Change in DLQI (week 12) (better indicated by lower values)											
1 PHOENIX1 – unpublish	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	serious[l]	none	207	296	-	MD 0.9 lower (2.11 lower to 0.31 higher)	⊕OOO VERY LOW

ed data											
Change in DLQI (week 12) (better indicated by lower values)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	serious[l]	none	243	560	-	MD 1 lower (2.07 lower to 0.07 higher)	⊕OOO VERY LOW
Change in DLQI (week 28) (better indicated by lower values)											
1 PHOENIX1 – unpublished data	observational studies	serious[d]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	204	286	-	MD 0.4 lower (1.71 lower to 0.91 higher)	⊕OOO VERY LOW
Change in DLQI (week 28) (better indicated by lower values)											
1 PHOENIX2 – unpublished data	observational studies	serious[e]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	238	555	-	MD 0.5 lower (1.6 lower to 0.6 higher)	⊕OOO VERY LOW
Change in DLQI (week 52) (better indicated by lower values)											
1 PHOENIX1 – unpublished data	observational studies	serious[f]	no serious inconsistency	no serious indirectness[b]	serious[c]	none	59	103	-	MD 1.6 lower (3.77 lower to 0.57 higher)	⊕OOO VERY LOW
Partial response (week 28)											
1 Papp 2008	observational studies	serious[m]	no serious inconsistency[g]	no serious indirectness[b]	serious[n]	none	307	513	Logistic regression analysis revealed that inadequate response to at least one biological agent was an independent predictor of partial response (p=0.024), as was a history of psoriatic arthritis (p=0.047) Partial responders were more likely than responders to have failed treatment with at least one		⊕OOO VERY LOW

									biological agent (12.1% of PASI75 responders vs 21.5% of partial responders)	

(a) ACCEPT study - similar baseline characteristics in those with and without prior exposure to biological therapy (including similar proportions receiving the low and high doses); but slightly longer disease duration (5.3 years), greater age (by 3.6 years) and proportion with marked to severe disease (by 5.4%) in those with prior biological exposure; and higher mean weight among those receiving the 45 mg dose in those with prior exposure (94.8 kg vs 90.0 kg). Acceptable dropout rate but unclear if different for those with and without prior biological exposure.

(b) Previous biological drugs included alefacept and efalizumab (proportions unclear)

(c) Confidence interval ranges from clinically important effect to no effect

(d) PHOENIX1: Those with and without prior exposure to biological therapy not matched on baseline characteristics (although similar proportions received the low and high doses): slightly longer disease duration (1.7 years), greater proportion male (by 5.3%), and greater disease severity (proportion with marked to severe disease in the 45 mg group 7.4% higher; PASI ≥20 13.6% higher; BSA≥20% 7.7% higher; DLQI 1.2 points higher) in those with prior biological exposure; and higher mean weight among those receiving the 45 mg dose in those with prior exposure (97.34 kg vs 91.12 kg). Acceptable dropout rate but unclear if different for those with and without prior biological therapy exposure

(e) PHOENIX2: Those with and without prior exposure to biological drugs not matched on baseline characteristics (although similar proportions received the low and high doses): slightly longer disease duration (2.8 years), and greater disease severity (proportion with marked to severe disease 11% higher; PASI ≥20 7.8% higher; BSA≥20% in the 90 mg group 8.7% higher; DLQI 1.4 points higher) in those with prior biological exposure; and higher mean weight among those receiving the 90 mg dose in those with prior exposure (94.45 kg vs 90.2 kg). Acceptable dropout rate but unclear if different for those with and without prior biological exposure

(f) PHOENIX1: Those with and without prior exposure to biological drugs not matched on baseline characteristics (although similar proportions received the low and high doses): slightly longer disease duration (1.7 years), greater proportion male (by 5.3%), and greater disease severity (proportion with marked to severe disease in the 45 mg group 7.4% higher; PASI ≥20 13.6% higher; BSA≥20% 7.7% higher; DLQI 1.2 points higher) in those with prior biological exposure; and higher mean weight among those receiving the 45 mg dose in those with prior exposure (97.34 kg vs 91.12 kg). Acceptable dropout rate but unclear if different for those with and without prior biological exposure; and only those with PASI75 response at week 28 and who continued on the same dose of ustekinumab up to week 52 were analysed

(g) PHOENIX2: Those with and without prior exposure to biological drugs not matched on baseline characteristics (although similar proportions received the low and high doses): slightly longer disease duration (2.8 years), and greater disease severity (proportion with marked to severe disease 11% higher; PASI ≥20 7.8% higher; BSA≥20% in the 90 mg group 8.7% higher; DLQI 1.4 points higher) in those with prior biological exposure; and higher mean weight among those receiving the 90 mg dose in those with prior exposure (94.45 kg vs 90.2 kg). Acceptable dropout rate but unclear if different for those with and without prior biological exposure; and only those with PASI75 response at week 28 and who continued on the same dose of ustekinumab up to week 52 were analysed

(h) Failure to adequately control for confounding (no matching for prognostic factors or adjustment in statistical analyses)

[9]10/80 who achieved PASI75 at week 16 received overlap therapy (CSA, MTX or acitretin) during induction; 4 of these were still on an additional systemic therapy at 16 weeks. Of these 10, 7 had had previous biological exposure and 3 were naïve to biological therapy. Also prior biologics included efalizumab (proportion unclear).

(i) Alefacept and efalizumab were included in the previous biological drugs used

(j) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect

(k) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit for a second biological therapy to no clinically important benefit)

(l) Unclear if adequately controlled for confounding by adjustment of statistic analyses

(m) Insufficient data to assess imprecision

13.2.7 Evidence statements

In people with psoriasis being treated with ustekinumab, those with no prior exposure to biological therapy had a statistically significantly better result than those with previous biological therapy exposure (including all definitions of this comparison) for:

- Clear/nearly clear (PASI90 or PGA) at 12 weeks [1 study; 820 participants; very low quality evidence][419]
- Clear/nearly clear (PASI90 or PGA) at 24 weeks [1 study; 800 participants; very low quality evidence][419]
- Clear/nearly clear (PASI90) at 52 weeks [1 study; 537 participants; very low quality evidence][419]
- PASI75 at 12 weeks [2 studies; 1331 participants; very low quality evidence][419,420]
- PASI75 at 24 weeks [1 study; 497 participants; very low quality evidence][419,420]
- Percentage improvement in PASI at 12 weeks [3 studies; 1861 participants; low to very low quality evidence][418-420]
- Percentage improvement in PASI at 24 weeks [1 study; 497 participants; very low quality evidence][418]
- Percentage improvement in PASI at 52 weeks [1 study; 537 participants; very low quality evidence][419]

Even though cases where those with no prior exposure to biological therapy had a statistically significantly better result, those who had previously received a biological drug still had substantial response rates (clear/nearly clear [PASI90]: 37.6, 46.7 and 58.1% at 12, 24 and 52 weeks, respectively; clear/nearly clear [PGA] at 24 weeks: 65.7%; PASI75: 60.4-63.2% and 66.5-74.9% at weeks 12 and 24, respectively; % improvement in PASI: 68.3-76.6%, 82.6% and 88.1% at weeks 12, 24 and 52, respectively).

In people with psoriasis being treated with ustekinumab, there was no statistically significant difference between those with and without prior exposure to biological therapy (including all definitions of this comparison) for:

- Clear/nearly clear (PASI90 or PGA) at 12 weeks [2 studies; 1066 participants; very low quality evidence][418,420]
- Clear/nearly clear (PASI90 or PGA) at 24 weeks [1 study; 497 participants; very low quality evidence][418]
- Clear/nearly clear (PASI90 or PGA) at 52 weeks [1 study; 162 participants; very low quality evidence][418]
- Clear/nearly clear (PGA) at 52 weeks [1 study; 537 participants; very low quality evidence][419]
- PASI75 at 12 weeks [1 study; 555 participants; very low quality evidence][420]
- PASI75 at 16 weeks [1 study; 127 participants; very low quality evidence][415,416]
- PASI75 at 24 weeks [1 study; 800 participants; very low quality evidence][419,420]
- PASI75 at 28 weeks [1 study; 802 participants; very low quality evidence][410]
- PASI75 at 52 weeks [2 studies; 699 participants; very low quality evidence][419,420]
- PASI50 at 12 weeks [3 studies; 1886 participants; very low quality evidence][418-420]
- PASI50 at 24 weeks [2 studies; 1297 participants; very low quality evidence][419,420]
- PASI50 at 52 weeks [2 studies; 699 participants; very low quality evidence][419,420]
- Percentage improvement in PASI at 24 weeks [1 study; 406 participants; very low quality evidence][419]

- Percentage improvement in PASI at 52 weeks [1 study; 162 participants; very low quality evidence][418]
- Change in DLQI at 12 weeks [2 studies; 1306 participants; very low quality evidence][419,420]
- Change in DLQI at 28 [2 studies; 1283 participants; very low quality evidence][419,420]
- Change in DLQI at 52 weeks [1 study; 162 participants; very low quality evidence][4184]

In one study[415] a sensitivity analysis was performed for the outcome of PASI75 removing those who had received overlap therapy from the analysis (see Appendix F). This did not change the overall relative effect, although the response rate was higher.

Evidence statements for Papp et al 2008 where no original analysis could be performed comparing those with and without prior exposure to biological therapy:

- There was a statistically significantly higher likelihood of having only a partial response (PASI50 but not PASI75) at 28 weeks on ustekinumab compared to a full (PASI75) response for those with prior exposure to biological therapy compared with those without prior exposure [1 study; 722 participants; very low quality evidence][410]

13.2.7.1 Subgroup analyses and heterogeneity

- One study[4156] presented the outcome of PASI75 for patients naïve to biological therapy compared with those who had any previous exposure to biological therapy and those with none or one prior biological drug compared with 2-4 prior biological drugs, both of which showed no significant difference. There was no inconsistency between these two subgroups.

13.3 Adalimumab as a first TNF antagonist vs adalimumab following discontinuation of a previous TNF antagonist

13.3.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Previous TNF antagonist	No previous TNF antagonist	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90: 16 weeks; any prior anti-TNF vs none)											

1 Ortonne 2011	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	103/282 (36.5%)	222/448 (49.6%)	RR 0.74 (0.62 to 0.88)	129 fewer per 1000 (from 59 fewer to 188 fewer)	⊕OOO VERY LOW
Clear/nearly clear (PGA: 16 weeks; any prior anti-TNF vs none)											
1 Ortonne 2011	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	149/282 (52.8%)	293/448 (65.4%)	RR 0.81 (0.71 to 0.92)	124 fewer per 1000 (from 52 fewer to 190 fewer)	⊕OOO VERY LOW
Clear or nearly clear PGA (week 16; failed prior etanercept vs failed prior non-biological agent)											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness[d]	serious[e]	none	40/77 (51.9%)	39/66 (59.1%)	RR 0.88 (0.66 to 1.18)	71 fewer per 1000 (from 201 fewer to 106 more)	⊕OOO VERY LOW
Clear or nearly clear PGA (week 16; failed prior etanercept vs failed prior non-biological agent) - primary non-responder											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness	very serious[f]	none	15/26 (57.7%)	28/45 (62.2%)	RR 0.93 (0.62 to 1.38)	44 fewer per 1000 (from 236 fewer to 236 more)	⊕OOO VERY LOW
Clear or nearly clear PGA (week 16; failed prior etanercept vs failed prior non-biological agent) - secondary non-responder											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness	very serious[f]	none	27/58 (46.6%)	9/23 (39.1%)	RR 1.19 (0.67 to 2.12)	74 more per 1000 (from 129 fewer to 438 more)	⊕OOO VERY LOW
PASI75 (week 16) - adjusted OR (any prior anti-TNF vs none)											
1 Ortonne 2011	observational studies	serious[g]	no serious inconsistency	serious[b,h]	serious[e]	none	174/282 (61.7%)	321/448 (71.7%)	OR 0.7 (0.5 to 1.1)	78 fewer per 1000 (from 158 fewer to 19 more)	⊕OOO VERY LOW
PASI75 (week 16) - RR (any prior anti-TNF vs none)											
1 Ortonne 2011	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	174/282 (61.7%)	321/448 (71.7%)	RR 0.87 (0.78 to 0.97)	93 fewer per 1000 (from 21 fewer to 158 fewer)	⊕OOO VERY LOW
Withdrawal due to lack of efficacy (week 16; any prior anti-TNF vs none)											
1 Ortonne	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[b]	very serious[f]	none	3/270 (1.1%)	5/414 (1.2%)	RR 0.92 (0.22 to 2.82)	1 fewer per 1000 (from 9 fewer to 22 more)	⊕OOO VERY LOW

2011											
Withdrawal due to lack of efficacy (week 16; failed prior etanercept vs failed prior non-biological agent)											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness[d]	very serious[f]	none	4/77 (5.2%)	3/66 (4.5%)	RR 1.14 (0.27 to 4.92)	6 more per 1000 (from 33 fewer to 178 more)	⊕OOO VERY LOW
Withdrawal due to toxicity (week 16; any prior anti-TNF vs none)											
1 Ortonne 2011	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[b]	no serious imprecision	none	5/272 (1.8%)	22/431 (5.1%)	RR 0.36 (0.14 to 0.94)	33 fewer per 1000 (from 3 fewer to 44 fewer)	⊕OOO VERY LOW
Withdrawal due to toxicity (week 16; failed prior etanercept vs failed prior non-biological agent)											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness[d]	very serious[f]	none	0/73 (0%)	1/64 (1.6%)	RR 0.29 (0.01 to 7.06)	11 fewer per 1000 (from 15 fewer to 95 more)	⊕OOO VERY LOW
Serious adverse events (16 weeks + 70 days post treatment; any prior anti-TNF vs none)											
1 Ortonne 2011	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[b]	very serious[f]	none	11/282 (3.9%)	20/448 (4.5%)	RR 0.87 (0.43 to 1.8)	6 fewer per 1000 (from 25 fewer to 36 more)	⊕OOO VERY LOW
Serious adverse events (16 weeks + 70 days post treatment; failed prior etanercept vs failed prior non-biological agent)											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness[d]	very serious[f]	none	4/82 (4.9%)	1/70 (1.4%)	RR 3.41 (0.39 to 29.85)	34 more per 1000 (from 9 fewer to 412 more)	⊕OOO VERY LOW
Change in DLQI (week 16; failed prior etanercept vs failed prior non-biological agent)											
1 Strober 2011	observational studies	very serious[c]	no serious inconsistency	no serious indirectness[d]	serious[i]	none	80	69		Etanercept (n=80) / Methotrexate (n=40) / NBUVB (n=29) *Screening mean*: *8.9* / *10.5* / *10.4* Change: -3.8 / -7.0 / -6.5	⊕OOO VERY LOW
Final DLQI (week 16; any prior anti-TNF vs none)											
1 Ortonne 2011	observational studies	serious[g]	no serious inconsistency	serious[b,j]	serious[k]	none	187	388		Prior TNF-antagonist (n=281) / No prior TNF-antagonist (n=446) / p-value*	⊕OOO VERY LOW

									Baseline	13.8	14.0	0.165	
									Week 16	4.5	3.4	0.199	
									Change	-9.3	-10.6		
									* ANCOVA adjusted for treatment group, number of prior non-biological systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.				

(a) Post hoc subanalysis of RCT data (study not designed or powered for this analysis); and groups not matched for % male, history of PsA or prior systemic treatments
(b) 3.6% of those previously using TNF antagonists were previously exposed to certolizumab
(c) Failure to adequately control for confounding (no matching for prognostic factors or adjustment in statistical analyses); not matched for sex (more males in methotrexate group), race (more whites in MTX group); duration of treatment with previous agent (longer with etanercept); higher disease severity in UVB group based on PGA and PASI; fewer with PsA in UVB group; higher drop out in UVB and etanercept groups
(d) PsA = 46.7%
(e) Confidence interval ranges from clinically important effect to no effect
(f) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect
(g) Post hoc subanalysis of RCT data (study not designed or powered for this analysis)
(h) Data based on pooled figures from those treated with adalimumab plus vehicle and adalimumab plus topical calcipotriol and betamethasone dipropionate (standard regimen)
(i) No SD provided
(j) Surrogate outcome for change in DLQI
(k) No data available to assess imprecision

13.3.2 Evidence statements

In people with psoriasis being treated with adalimumab, those with no prior exposure to TNF antagonist therapy had a statistically significantly better result than those with previous TNF antagonist exposure (including all definitions of this comparison) for:

- Clear or nearly clear (PASI90 and PGA) at 16 weeks [1 study; 730 participants; very low quality evidence][411]
- PASI75 at 16 weeks (risk ratio) [1 study; 730 participants; very low quality evidence][411]

Even in these cases where those with no prior exposure to biological therapy had a statistically significantly better result, those who had previously received a biological drug still had substantial response rates (37.4% PASI90, 52.8% clear/nearly clear on PGA; 53.7% PASI75).

In people with psoriasis being treated with adalimumab, those with prior exposure to TNF antagonist therapy had a statistically significantly better result than those with **no** previous TNF antagonist exposure for:

- Withdrawal due to toxicity at 16 weeks [1 study; 703 participants; very low quality evidence][411]

In people with psoriasis being treated with adalimumab, there was no statistically significant difference between those with and without prior exposure to TNF antagonist therapy (including all definitions of this comparison) for:

- Clear/nearly clear (PGA) at 16 weeks [1 study; 143 participants; very low quality evidence][414]
- Clear/nearly clear (PGA; primary and secondary non-responders*) at 16 weeks [1 study; 152 participants; very low quality evidence][421]
- PASI75 at 16 weeks (full group – adjusted odds ratio) [1 study; 730 participants; very low quality evidence][411]
- Final DLQI at 16 weeks [1 study; 727 participants; very low quality evidence][411]
- Withdrawal due to lack of efficacy at 16 weeks [2 studies; 827 participants; very low quality evidence][411;414]
- Withdrawal due to toxicity at 16 weeks [1 study; 137 participants; very low quality evidence][414]
- Serious adverse events at 16 weeks plus up to 70 days post-treatment follow-up [2 studies; 882 participants; very low quality evidence][411;414]

The Ortonne study[411] included people who had been treated with previous biological drugs, not only those who had failed to respond to previous biological drugs, while the Strober study[414] included those who had failed prior etanercept compared with those who had failed prior conventional therapies.

This was a based on a sub-analysis of the same sample included in another study[414], and some participants were counted in both primary and secondary non-responder groups because they reported having had both primary and secondary non-responses.

Evidence statement for one study where no original analysis could be performed comparing adalimumab as a first biological drug and adalimumab following failure of etanercept:

- There was a greater change in DLQI from baseline to week 16 in those without previous exposure to biological therapy than in those who had previously used etanercept [1 study; 149 participants; very low quality evidence][414]

13.3.261 Subgroup analyses and heterogeneity

- One study[421] presented the response rates among primary and secondary non-responders to prior biological therapy, as well as for those with no prior exposure to biological therapy. There were no statistically significant subgroup differences between primary and secondary non-responders compared to those with no prior exposure for the outcome of clear or nearly clear assessed on the PGA.
- One study[411] presented the response rates on adalimumab among those with and without exposure to a previous TNF antagonist separately for those with and without concomitant psoriatic arthritis.

There were no significant subgroup differences on the outcomes of:

  - PASI75 at week 16 (although the I^2 statistic indicating heterogeneity was close to the threshold of 50%; $I^2 = 44\%$) and the PsA subgroup more strongly favoured those with no previous exposure to biological therapy)
  - Clear or nearly clear at week 16

It was unclear whether there were differences at baseline between those with and without concomitant PsA, although there were similar proportions with PsA in both the previous exposure and no previous exposure to TNF antagonist groups.

Adjusted subgroup analyses

One study[411] presented the response rates on adalimumab based on information about the prior exposure characteristics adjusted for relevant confounders (see Table 174).

13.353 Evidence profile

Quality assessment							No of patients	Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute	
Response										
1 Ortonne 2011	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	See Table 174			⊕OOO VERY LOW

(a) No data available to assess imprecision

Table 174: Summary of data from adjusted regression analysis comparing response rates in people treated with adalimumab between various characteristics of previous TNF antagonist exposure vs no previous exposure

Study	Total N	Follow-up	Result					Group favoured	Quality
Prior anti-TNF agent									
Ortonne 2011	671	16 weeks		Patients (%)			p-value vs no prior TNF antagonist	No prior TNF-antagonist (NS)	VERY LOW
				No prior TNF-antagonist (n=448)	Prior etanercept (n=170)	Prior infliximab (n=53)			
			PASI75	321 (71.7%)	111 (65.3%)	31 (58.5%)	ETA = 0.361 INF = 0.174		
			PASI90	222 (49.6%)	63 (37.1%)	18 (34.0%)	ETA = 0.051 INF = 0.118		
			PASI100	102 (22.8%)	25 (14.7%)	8 (15.1%)	ETA = 0.173 INF = 0.576		
			PGA clear or minimal	293 (65.4%)	97 (57.1%)	25 (47.2%)	ETA = 0.385 INF = 0.058		

Study	Total N	Follow-up	Result					Group favoured	Quality
Number of prior anti-TNF treatments									
Ortonne 2011	671	16 weeks		Patients (%)			p-value vs no prior TNF antagonist	No prior TNF-antagonist (NS and SS)	VERY LOW
				No prior TNF-antagonist (n=448)	1 prior TNF-antagonist (n=231)	≥2 TNF-antagonist (n=51)			
			PASI75	321 (71.7%)	149.0 (64.5%)	25.0 (49.0%)	1 = 0.234 ≥2 = 0.016		
			PASI90	94 (49.6%)	84.1 (36.4%)	19.0 (37.3%)	1 = 0.021 ≥2 = 0.276		
			PASI100	144 (22.8%)	34.0 (14.7%)	8.0 (15.7%)	1 = 0.166 ≥2 = 0.766		
			PGA clear or minimal	170 (65.4%)	128.0 (55.4%)	21.0 (41.2%)	1 = 0.176 ≥2 = 0.026		
Reason for discontinuation of prior anti-TNF treatments									
Ortonne 2011	671	16 weeks		Patients (%)				No prior TNF-antagonist (NS and SS)	VERY LOW
				No prior TNF-antagonist (n=448)	Prior TNF-antagonist (n=282)	Never responded (n=80)	Lost response (n=99)	Intolerance (n=16)	
			PASI75	321 (71.7%)	174 (61.7%) p=0.095	43 (53.8%) p=0.006	65 (65.7%) p=0.673	8 (50.0%) p=0.213	

13.3.14 Evidence statements

In people with psoriasis, there was no statistically significant difference in response to adalimumab between those with no prior exposure to TNF antagonist therapy and those with previous exposure specifically to either etanercept or infliximab for:

- PASI75, PASI90, PASI100 or PGA clear/minimal at 16 weeks [1 study; 618 and 501 participants for etanercept and infliximab, respectively; very low quality evidence][411]

In people with psoriasis treated with adalimumab, those with no prior exposure to TNF antagonist therapy had a statistically significantly greater response than those with previous exposure specifically to one or at least two previous TNF antagonists for:

- One prior TNF antagonist:
  - PASI90 at 16 weeks [1 study; 679 participants; very low quality evidence][411]
- At least 2 prior TNF antagonists:
  - PASI75 or PGA clear/minimal at 16 weeks [1 study; 499 participants; very low quality evidence][411]

In people with psoriasis treated with adalimumab, there was no statistically significant difference between those with no prior exposure to TNF antagonist therapy and those with previous exposure specifically to one or at least two previous TNF antagonists for:

- One prior TNF antagonist:
  - PASI75, PASI100 or PGA clear/minimal at 16 weeks [1 study; 679 participants; very low quality evidence][411]
- At least 2 prior TNF antagonists:
  - PASI90 or PASI100 at 16 weeks [1 study; 499 participants; very low quality evidence][411]

In people with psoriasis treated with adalimumab, those with no prior exposure to TNF antagonist therapy had a statistically significantly greater response than those with previous exposure who never responded for:

- PASI75 at 16 weeks [1 study; 528 participants; very low quality evidence][411]

In people with psoriasis treated with adalimumab, there was no statistically significant difference between those with no prior exposure to TNF antagonist therapy and those with previous exposure who lost response or were intolerant to the TNF antagonist for:

- PASI75 at 16 weeks [1 study; 547 or 464 participants, for lost response and intolerant, respectively; very low quality evidence][411]

13.4 Infliximab vs. placebo in those with prior exposure to biological therapy

13.4.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab	Placebo	Relative (95% CI)	Absolute	
PASI 75 (week 10) - previous biological therapy											

1 Menter 2010	randomised trials	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	68/94 (72.3%)	0/27 (0%)	RR 40.38 (2.58 to 631.5)	-	⊕⊕OO LOW

(a) Post-hoc subgroup analysis (study not designed or powered for this analysis). Drop-out rate <20% in both arms but twice as high in the placebo group

(b) Follow-up only 10 weeks (BNF suggests discontinuation if no response after 14 weeks)

13.4.2 Evidence statement

In people with psoriasis, infliximab was statistically significantly better than placebo in both those with prior exposure to biological therapy for:

- PASI75 at 10 weeks [1 study; 121 participants; low quality evidence][412]. This study stated only that people had been treated with previous biological drugs, and not whether they had failed to respond to this prior treatment. It was unclear which biological drugs were used previously.

13.5 Ustekinumab vs placebo in those with prior exposure to biological therapy

13.5.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ustekinumab	Placebo	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90; week 12)											
2 Phoenix 1&2 - unpublished	randomised trials	serious[l,b]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	169/462 (36.6%)	1/229 (0.44%)	RR 56.12 (11.34 to 277.82)	241 more per 1000 (from 45 more to 1000 more)	⊕⊕⊕O MODERATE
Clear/nearly clear (PGA; week 12)											
2 Phoenix 1&2 - unpublished	randomised trials	serious[l,b]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	284/462 (61.5%)	5/229 (2.2%)	RR 28.16 (11.8 to 67.19)	593 more per 1000 (from 236 more to 1000 more)	⊕⊕⊕O MODERATE
PASI75 (week 12)											
2 Phoenix 1&2 - unpublished	randomised trials	serious[l,b]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	286/462 (61.9%)	4/229 (1.7%)	RR 31.61 (12.63 to 79.11)	535 more per 1000 (from 203 more to 1000 more)	⊕⊕⊕O MODERATE

PASI50 (week 12)											
2 Phoenix 1&2 - unpublished	randomised trials	serious[l,b]	serious[d]	no serious indirectness[c]	no serious imprecision	none	384/462 (83.1%)	10/229 (4.4%)	RR 20.42 (6.43 to 64.86)	848 more per 1000 (from 203 more to 1000 more)	⊕⊕OO LOW
% improvement in PASI (week 12) (better indicated by higher values)											
2 Phoenix 1&2 - unpublished	randomised trials	serious[l,b]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	456	228	-	MD 75.9 higher (71.33 to 80.47 higher)	⊕⊕⊕O MODERATE
Change in DLQI (week 12) - lower baseline DLQI (better indicated by lower values)											
1 Phoenix 1 - unpublished	randomised trials	serious[b,e]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	207	105	-	MD 9.04 lower (10.51 to 7.57 lower)	⊕⊕⊕O MODERATE
Change in DLQI (week 12) - higher baseline DLQI (better indicated by lower values)											
1 Phoenix 2 - unpublished	randomised trials	serious[b,f]	no serious inconsistency	no serious indirectness[c]	no serious imprecision [g]	none	243	123	-	MD 10.6 lower (11.85 to 9.35 lower)	⊕⊕⊕O MODERATE

(a) Baseline characteristics similar among those randomised to placebo and ustekinumab who had previously received a biological drug (although in PHOENIX 1 slightly higher proportion male (by 6.9%), longer disease duration (by 1.8 years) and greater disease severity (10.1% more with BSA≥20%, but mean PASI, mean BSA and proportion marked or severe on PGA were all very similar) in placebo group and in PHOENIX 2 slightly higher proportion male (by 6.2%), age (by 3 years), weight (by 5.4 kg - but mean >90 kg in both groups) and greater disease severity (6.1% more with BSA≥20% and 4.9% more with marked or severe on PGA, but mean PASI and mean BSA and were very similar) in placebo group)

[2] Post-hoc subgroup analysis (study not designed or powered for this analysis)

(b) Previous biological drugs included alefacept and efalizumab (proportions unclear)

(c) Unexplained heterogeneity (I^2 = 59%)

(d) PHOENIX 1 - baseline characteristics similar among those randomised to placebo and ustekinumab who had previously received a biological drug (although slightly higher proportion male (by 6.9%), longer disease duration (by 1.8 years) and greater disease severity (10.1% more with BSA ≥20%, but mean PASI, mean BSA and proportion marked or severe on PGA were all very similar) in placebo group

(e) PHOENIX 2 - baseline characteristics similar among those randomised to placebo and ustekinumab who had previously received a biological drug (although slightly higher proportion male (by 6.2%), age (by 3 years), weight (by 5.4 kg - but mean >90 kg in both groups) and greater disease severity (6.1% more with BSA≥20% and 4.9% more with marked or severe on PGA, but mean PASI and mean BSA and were very similar) in placebo group

(f) Precise according to GDG discussion (confidence interval lies completely within effect estimates that indicate clinically important benefit)

13.5.2 Evidence statements

In people with psoriasis who have been treated with at least one biological drug, ustekinumab was statistically significantly better than placebo for:

- Clear or nearly clear (PASI90 and PGA) at 12 weeks [2 studies; 691 participants; moderate quality evidence][418,419]
- PASI75 at 12 weeks [2 studies; 691 participants; moderate quality evidence][418,419]
- PASI50 at 12 weeks [2 studies; 691 participants; low quality evidence][418,419]
- Percentage improvement in PASI at 12 weeks [2 studies; 684 participants; moderate quality evidence][418,419]
- Change in DLQI at 12 weeks [2 studies; 678 participants; moderate quality evidence][418,419]

13.5.261 Heterogeneity

Significant heterogeneity was found between the two studies available for this comparison on the outcomes of PASI50 and change in DLQI. The heterogeneity for PASI50 could not be explained, while the difference in the change in DLQI was thought to be due to the difference in baseline DLQI (the score was higher in the study[419] that showed the greater improvement).

13.6 Ustekinumab vs etanercept in those with prior exposure to biological therapy

13.6.21 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ustekinumab	Etanercept	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90; week 12)											
1 ACCEPT – unpublished data	randomised trials	very serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	10/36 (27.8%)	4/27 (14.8%)	RR 1.88 (0.66 to 5.34)	130 more per 1000 (from 50 fewer to 643 more)	⊕OOO VERY LOW
Clear/nearly clear (PGA; week 12)											
1 ACCEPT – unpublish	randomised trials	very serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	19/36 (52.8%)	10/27 (37%)	RR 1.43 (0.8 to 2.55)	156 more per 1000 (from 74 fewer to 574 more)	⊕OOO VERY LOW

ed data											
PASI75 (week 12)											
1 ACCEPT – unpublished data	randomised trials	very serious[a]	no serious inconsistency	serious[b]	serious[d]	none	20/36 (55.6%)	10/27 (37%)	RR 1.5 (0.85 to 2.66)	185 more per 1000 (from 56 fewer to 615 more)	⊕OOO VERY LOW
PASI50 (week 12)											
1 ACCEPT – unpublished data	randomised trials	very serious[a]	no serious inconsistency	serious[b]	very serious[e]	none	28/36 (77.8%)	20/27 (74.1%)	RR 1.05 (0.79 to 1.39)	37 more per 1000 (from 156 fewer to 289 more)	⊕OOO VERY LOW
% improvement in PASI (week 12) (Better indicated by higher values)											
1 ACCEPT – unpublished data	randomised trials	very serious[a]	no serious inconsistency	serious[b]	serious[d]	none	35	27	-	MD 2.75 higher (11.58 lower to 17.08 higher)	⊕OOO VERY LOW

(a) Post-hoc subgroup analysis (study not designed or powered for this analysis). Unclear allocation concealment and single blind; not matched for baseline characteristics (6.4% more male, 2.8 kg lighter, 4 years shorter duration and less severe disease (mean BSA 5.6% lower and 11.6% fewer with marker or severe disease on PGA) in etanercept group)

(b) Indirect comparison (benefit of different biological drugs in those who have previously received another biological drug). Also, high dose of etanercept (50 mg twice weekly). Previous biologicals included alefacept and efalizumab (proportions unclear)

(c) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect

(d) Confidence interval ranges from clinically important effect to no effect

(e) Very serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit for one intervention to clinically important benefit for the other intervention)

13.6.2 Evidence statements

In people with psoriasis who have been treated with at least one prior biological drug, there was no statistically significant difference between ustekinumab and etanercept for:

- Clear/nearly clear (PASI90 or PGA) at 12 weeks [1 study; 63 participants; very low quality evidence][420]
- PASI75 at 12 weeks [1 study; 63 participants; very low quality evidence][420]
- PASI50 at 12 weeks [1 study; 63 participants; very low quality evidence][420]

- % improvement in PASI at 12 weeks [1 study; 62 participants; very low quality evidence][420]

13.7 Economic evidence

13.7.1 Literature review

No relevant economic evidence was identified.

13.7.2 Original economic analysis

The GDG considered the clinical evidence reviewed as part of the guideline to suggest that patients who have previously been treated with a biological therapy may benefit from switching to a second biological therapy; however, this strategy is also associated with very high costs to the NHS.

No cost-effectiveness analyses were identified from the published literature nor were any provided during the call for evidence. The GDG considered the sequential use of biological therapy to be a high priority for original economic analysis given the current variation of its provision to patients with psoriasis in the NHS, the high cost of these agents and the limited range of alternative treatments available to this small group of patients.

Below is a summary of the analysis that was undertaken. For full details please see Appendix O.

Methods used were broadly similar to those of the NICE technology appraisals except that:

- The GDG felt previous TA analyses underestimated resource use of 'best supportive care' (BSC) and this would be especially true for this population who are likely to have more severe disease. This is outlined in Appendix P in which we described various costing/resource use studies and defined BSC. Our costs for BSC were £10,700 compared with £5300 in the TAs – the difference was mainly due to additional hospital stay (£2000), day centre visits (£1800) and drugs (£1100).
- We assumed a class effect for all biologics because evidence was lacking for all the individual drugs (subgroup analyses only available for ustekinumab and infliximab, not etanercept or adalimumab). Also we could not find the evidence to assess whether the effect of a particular second-line biologic is dependent on exactly which drug failed first-line.

13.7.3 Methods

The analysis was undertaken to evaluate the cost-effectiveness of switching to a second biological drug compared to best supportive care for patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biological therapy. A Markov model was used to estimate 10-year costs and quality-adjusted life years (QALYs) from a current UK NHS and personal social services perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance. Uncertainty was explored through probabilistic analysis and extensive sensitivity analyses.

The population used for the analysis was people with moderate to severe chronic plaque psoriasis who have been previously treated with biological therapy. The clinical data available to inform the economic analysis did not allow for subgroup analyses to be performed based on the reason for failure of previous biological drug. Therefore, the population modelled includes primary non-responders (i.e. patients who had an insufficient response to a previous biological drug), secondary non-responders (i.e. patients who initially responded to previous biological therapy but lost that response over time) and patients who were intolerant to previous biological therapy.

The aim of the analysis was to assess the cost-effectiveness of biological therapy compared to best supportive care in the treatment of patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biological therapy. Due to a scarcity of data for specific

biological therapies including adalimumab, etanercept, infliximab and ustekinumab, the analysis assumes a class effect for biological agents. On that basis, the analysis could not look at particular sequences of biological agents and instead included the following comparators:

- Biological therapy
- Best supportive care

The probabilities of achieving different categories of PASI response were estimated by pooling all available placebo-controlled trials of biological therapies in an ordered probit model in WinBUGS.

A two part model was constructed in TreeAge Pro 2009 to capture the different costs and effects associated with biological therapy and best supportive care. The structure of the model was adapted from the model developed by Woolacott and colleagues[276], which has been used to inform related NICE guidance[7-10].

For the biological therapy arm, there was assumed to be a short 'trial' period, during which all hypothetical patients receive treatment and some level of benefit from treatment, and a 'treatment' period, during which only a subset of responders continue treatment and receive benefit. A schematic of the model pathway is presented in Figure 8.

'Trial' period:

- Hypothetical patients enter the model and receive a biological therapy for an initial 'trial period.'
- During this 'trial period' they achieve a given level of PASI response (<PASI50, PASI50 to PASI75, PASI75 to PASI90, >PASI90)

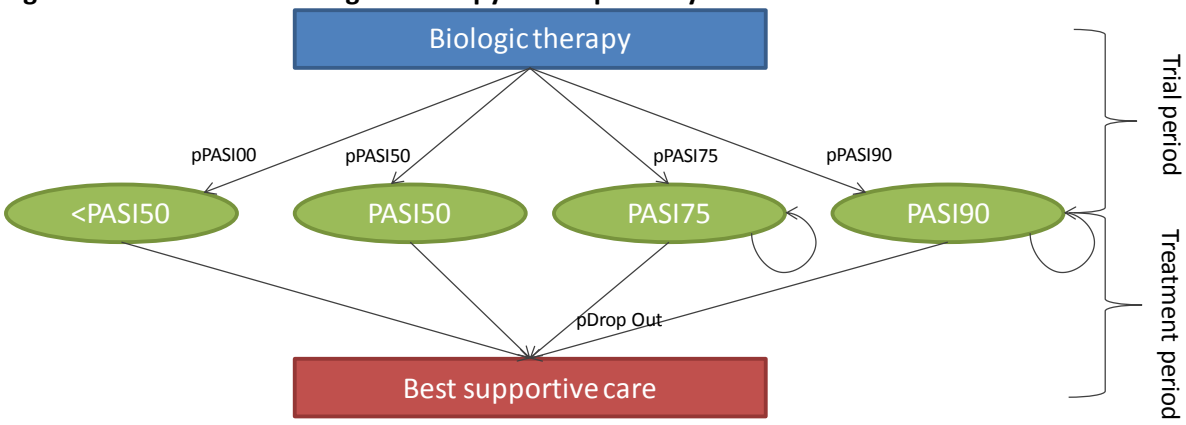
'Treatment' period:

- Patients who achieve a response >PASI75 continue treatment and maintain that level of response until they drop out at some point in the future
- Patients who achieve a response of <PASI75 discontinue treatment and move to best supportive care.

Key structural assumptions:

- Patients only receive benefit while they receive treatment, which is based on the assumption that treatments do not alter the progression of the disease
- Patients receiving treatment in the long term make no transitions between different levels of PASI response (i.e. they are assumed to maintain the same level of response observed at the end of the 'trial' period)

Figure 8: Second-line biological therapy model pathway



Best supportive care, which comprised of a combination of systemic non-biological therapies, UVB, complex topicals delivered in day centre care and inpatient stays, was assumed to vary in terms of the benefits it afforded patients. In the base case, effectiveness of best supportive care was assumed to be based on the placebo response data from the clinical review. This was tested in a series of one-way sensitivity analyses in which the effectiveness of best supportive care was varied first to assume that best supportive care was not at all effective (0% response), and then to match response data measured in a UK observational study by Woods and colleagues[422].

The cost of biological therapy took into account drug costs, administration costs, monitoring costs and outpatient visit costs and was split between the 'trial' period and 'treatment' periods. The cost of best supportive care took account of annual drug costs, monitoring costs, outpatient visits, phototherapy sessions, day centre sessions and inpatient stays. Defining best supportive care in terms of resource use was a challenge as no data were available for a group of patients who have failed treatment with an initial biological therapy.

The GDG judged the definition of only 2 outpatient visits per year, used by Woolacott and colleagues[276] for the evaluation of etanercept and efalizumab, to be a gross underestimate if applied to the population considered in the NCGC model. On the basis of some UK audit data and recent cost comparison studies,[422-424] the GDG came up with a working definition of best supportive care, which is detailed in Appendix P and summarised in Table 175.

Table 175: Assumed resource use for best supportive care

	Total annual cost			
Component	**Proportion receiving**	**Resource use components**		**Total Cost**
Drugs				
Methotrexate	45% (a)			£228
Ciclosporin (b)	45% (a)			£1,107
No drug	10% (a)	5 OP visits		£41
Other treatment				
Day centre care	100% (a)	5 visits		£1,813
NBUVB	16% (c)	1 course	24 sessions	£327
Inpatient care (g)				
High need	82% (d)	1 admission (a)	20.8 days per admission (f)	£4,625
Very high need	18% (d)	2.55 admissions (e)		£2,589
TOTAL				**£10,730 (h)**

(a) Based on GDG opinion
(b) Maximum treatment 2 years; after 2 years then no drug
(c) Based on proportion receiving PUVA in year before starting biological therapy in Driessen and colleagues[423]
(d) Based on split in Driessen and colleagues(under/over 30 days in hospital per annum)
(e) Calculated based on mean LOS from Woods[422] (20.8) and mean in hospital days per annum in the very high need group in Driessen[423] (53.0).
(f) Based on mean LOS for patients admitted with baseline PASI 10 to 20 in Woods[422]. 23.7 days used in sensitivity analysis.
(g) Weighted average length of stay equals 26.6 days per year per patient (20.8[0.82*1+0.18*2.55]=26.6) and weighted average cost equals £7,214 per patient.*
(h) Note: previous TAs[7-10] have estimated this cost to be approximately £5,327.71 (21 days in hospital + 2 outpatient visits per annum)

All model inputs were based on the clinical effectiveness review undertaken for the guideline, other published data and expert opinion, where required. These are described in full in the technical report in Appendix O. All model inputs and assumptions were validated by the GDG.

13.7.4 Results

Results of the base case suggest that compared to best supportive care, a second line biological therapy is likely to be cost effective at willingness to pay threshold of £20,000 per QALY gained. Results of the incremental analysis are presented in Table 176.

Table 176: Incremental analysis of base case results

Strategy	Total Costs	Incremental Cost	Total Benefit (QALYs)	Incremental Benefit (QALYs)	ICER (£/QALY)
BSC	£87,155		0.478		
Biologic	£90,661	£3,506	0.804	0.326	£10,755

Results indicate that switching to a second biological agent following intolerance to or failure of a first biological agents likely to cost £3,506 more over 10 years than switching to best supportive care, but this cost is likely to be offset by a 0.326 gain in QALYs. The incremental cost-effectiveness ratio (ICER) of second biological agent compared to best supportive care is £10,755 per QALY, a value well below the NICE willingness to pay threshold range of £20,000 to £30,000 per QALY gained.

The conclusion that switching to a second biological drug was tested in a wide range of sensitivity analyses, varying inputs related to biological agent and supportive care effectiveness, utility values, costs and estimates of resource use. The conclusions were relatively insensitive to changes in available utility values and reasonable assumptions about the annual drop out rate for ongoing biologic therapy. The conclusion of cost-effectiveness was somewhat sensitive to the assumed cost of the average biological therapy. When the cost was assumed to be that of infliximab, then switching to biological therapy was unlikely to be cost-effective; however, when it was assumed to be that of etanercept, adalimumab or ustekinumab only the conclusion was even stronger than in the base case.

The cost-effectiveness of switching to a second biological drug compared to best supportive care was quite sensitive to the assumed effectiveness of best supportive care (summarised in Table 177). If it was assumed to match the placebo response rates from the trials, the conclusion that biological therapy is cost-effective was unchanged. However, if PASI50 response rates to inpatient treatment observed in Wood and colleagues[422] were assumed, then the cost-effectiveness of a second biological drug was more uncertain.

Table 177: Results of sensitivity analyses around response rates for best supportive care

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
Placebo response from trials	£10,451	90%	99%
65% response rate (Woods 2008)	£22,411	24%	48%
83% response rate (Woods 2008)	£31,892	16%	24%

Further sensitivity analyses around the estimates of resource assumed for best supportive care showed the conclusion about the cost-effectiveness of sequential biological therapy to be highly uncertain (Table 178). The cost-effectiveness of switching to a second biological drug improves if

mean length of stay per admission increases and if a greater proportion of patients are classified as very high need (thus requiring more inpatient admissions per year). The likelihood that switching to a second biological drug is cost-effective decreases if the proportion of very high need patients decreases, the number of hospitalisations decreases and the other types of care in best supportive care are removed (i.e. no UVB, no day centre, no drugs). Under these reduced resource use assumption, switching to a second biological drug is only cost effective if patients are assumed to have the worst DLQI at baseline (that is, they have the most to gain from successful treatment).

Table 178: Results of sensitivity analyses around resource use inputs for best supportive care

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
No drugs in BSC	£9,307	93%	99%
Longer LOS (23.7 days)	£5,137	100%	100%
30% very high need	£3,306	100%	100%
5% very high need	£18,694	45%	81%
0.25 hospitalisations for high need and 2.55 hospitalisations for very high need (match Driessen 2010)	£35,079	7%	25%
0.5 hospitalisations for high need and 2 hospitalisations for very high need	£30,944	10%	35%
1 hospitalisation for all	£21,926	30%	69%
0.312 hospitalisations for all (match Fonia 2010)	£49,575	2%	8%
No hospitalisations	£60,998	1%	5%
1 hospitalisation for all and no drugs	£20,369	37%	75%
1 hospitalisation and 5 outpatient visits per year	£35,259	7%	25%
1 hospitalisation and 5 outpatient visits per year and 4th Quartile DLQI	£19,391	43%	77%

13.795 Limitations

In assessing the cost-effectiveness of biological therapy in patients with moderate to severe psoriasis who have previously been treated with biological therapy, no information was available from the published economic literature. It was therefore considered a priority to undertake original evaluation for the guideline in order to inform guideline recommendations. This analysis suggests that switching to a second line biological drug is potentially cost-effective compared to a strategy of best supportive care without biological therapy. Uncertainties in the analysis were explored through extensive sensitivity analysis which changed the conclusion in some cases, namely those in which best supportive care was assumed to produce some clinical and quality of life improvements or was assumed to be less resource intensive in terms of inpatient stays and other forms of hospital-based care (e.g. UVB, day centre treatments).

Most parameters in the model are highly uncertain which makes the analysis quite exploratory and interpretation a challenge. The clinical evidence for biological treatments evaluated in this population is limited, although it clearly shows there to be a benefit compared to placebo. However, in reality, this population would never receive simply a placebo. In the absence of biological therapy, they would likely receive a package of care with multiple components which may or may not produce quality of life benefits. Defining this package of care was a real challenge, and the analysis relied on a mixture of evidence from recent cost-analyses and GDG opinion. Indeed, efficacy and resource use

associated with best supportive care in the absence of biological therapy were among the most significant drivers of uncertainty in the analysis.

In terms of the population, the clinical evidence is quite muddled with no distinctions between patients who were primary or secondary treatment failures, intolerant to treatment or simply switched as part of a clinical trial. There is also uncertainty as to whether these patients have more, less or equally severe psoriasis as patients who are naïve to biological therapy. The GDG considered it likely that this group would have more severe, treatment-resistant disease and would thus represent a very resource-intensive group as well as one with a great deal to gain in terms of quality of life if treatment was successful.

As has been outlined in previous appraisals of biological therapy, there is relatively limited long-term experience with biological therapies, and thus estimates of drop out and sustained remission are based on assumptions. There was also limited data on adverse events, both in terms of their incidence as well as their impact on resource use and quality of life. These were excluded from the NCGC analysis, but the GDG did not think that this would change conclusions.

13.7.551 Economic evidence statements

New economic analysis from a current UK NHS and PSS perspective comparing biological therapy to best supportive care found that further biological therapy is likely to offer better value for NHS resources in the treatment of patients with moderate to severe plaque psoriasis who have previously been exposed to biological therapy and either failed to respond, lost response or were intolerant to this initial biological therapy. There is substantial uncertainty in this conclusion, which was explored through extensive sensitivity analyses around various parameters.

- Sensitivity analyses in which the cost of biological therapy was assumed to be very high (e.g. the cost of infliximab) found that switching to an alternative biological therapy was unlikely to be cost effective compared to best supportive care.
- Sensitivity analyses in which the cost of best supportive care was assumed to be lower than in the base case (due to fewer very high need patients, fewer hospitalisations, shorter length of stay or fewer visits to day care centre) or when it was more effective than in the base case found that switching to an alternative biological therapy was unlikely to be cost effective compared to best supportive care.
- Sensitivity analysis in which patients were assumed to start treatment with the worst baseline quality of life, and therefore had the most to gain from successful treatment, found that further biological therapy was likely to be more cost effective even when resource use for best supportive care was assumed to be low.

13.8 Recommendations and link to evidence

Recommendations	
Recommendations from 'Adalimumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 146).]	**96. Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met.** • **The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10.** • **The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is**

	intolerant of, or has a contraindication to, these treatments. **97. Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:** • **a 75% reduction in the PASI score (PASI 75) from when treatment started or** • **a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.** **98. When using the DLQI, healthcare professionals should ensure that when reaching conclusions on the severity of plaque psoriasis they take into account a person's disabilities (such as physical impairments) and linguistic or other communication difficulties. In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of adalimumab in accordance with recommendation 97.**
Recommendations are from 'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103).	**99. Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.** • **The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10.** • **The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments.** **100. Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:** • **a 75% reduction in the PASI score from when treatment started (PASI 75) or** • **a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.** **101. It is recommended that the use of etanercept for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.**
Recommendations from 'Infliximab for the treatment of adults with	**102. Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.**

psoriasis' (NICE technology appraisal guidance 134).	• **The disease is very severe as defined by a total PASI of 20 or more and a DLQI of more than 18.** • **The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments.** **103. Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:** • **a 75% reduction in the PASI score from when treatment started (PASI 75) or** • **a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.** **104. When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with recommendation 103.**
Recommendations are from 'Ustekinumab for the treatment of adults with moderate to severe psoriasis' (NICE technology appraisal guidance 180)	**105. Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met.** • **The disease is severe, as defined by a total PASI score of 10 or more and a DLQI score of more than 10.** • **The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA, or the person is intolerant of or has a contraindication to these treatments.** • **The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.** **106. Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:** • **a 75% reduction in the PASI score (PASI 75) from when treatment started or** • **a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started.** **107. When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.**

Recommendations	**108. Consider changing to an alternative biological drug in adults with psoriasis in whom there is an inadequate response to a first biological drug (either following the first 3 months of treatment [primary failure], or following an initially adequate response [secondary failure]), or if the first biological drug cannot be tolerated or becomes contraindicated.** **109. For adults in whom there is an inadequate response to a second biological drug, seek supra-specialist advice from a clinician with expertise in biological therapy.** **110. If a person has both psoriasis and psoriatic arthritis, take into account both conditions before making changes to biological therapy and manage their treatment in consultation with a rheumatologist. For further information see 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal guidance 199).**
Future research recommendations	**24. In people with psoriasis being treated with systemic non-biological or biological therapies what clinical or other markers prevent optimal treatment outcomes?** **25. In people with psoriasis, does early intervention to achieve and maintain complete disease remission alter the long term prognosis in terms of psoriasis severity, comorbidities (including psoriatic arthritis), or treatment-related adverse effects and are there any clinical (for example, demographic, phenotypic) or laboratory (for example genetic or immune markers) that can be used to identify those most likely to benefit from this treatment approach?**
Relative values of different outcomes	The key outcomes were agreed to be PASI50 and change in DLQI in line with existing NICE guidance and expert clinical opinion. No data were available for time to remission or time to relapse.
Trade off between clinical benefits and harms	There is a definite clinical benefit of a second biological drug, especially when compared to no care; however there is no robust evidence to recommend using biological drugs in a particular order. Overall the benefits of recommending a second biological drug in this very high need group of patients were felt to outweigh the potential harms of not doing so. The benefits of a second biological drug are disease control and improved quality of life, avoidance of exposure to serious adverse effects of other therapies previously discontinued due to toxicity, health care savings (best supportive care is not a zero cost option, see 'economic considerations' below), and equality of access to biological drugs compared to other inflammatory diseases such as rheumatoid arthritis. The harms are reduced efficacy of a second biological drug compared

	to a first, lack of long term treatment efficacy outcomes and therefore possibly only short term benefit, and high drug acquisition costs.
Economic considerations	There was no economic evidence from the published literature to inform the GDG on the cost-effectiveness of offering a second biological drug to patients with moderate to severe psoriasis who have not responded to, lost response to or been intolerant to a first biological drug. Original decision modelling undertaken for the guideline showed that switching to a second biological drug may be more cost-effective than moving to best supportive care without biological therapy, but there was substantial uncertainty surrounding this conclusion. Uncertainty was driven by unknowns regarding the definition and efficacy of best supportive care. The GDG considered definitions of best supportive care from previous economic analyses in the UK and found that the defined resource use was likely to be a gross underestimate. Based on the NICE eligibility criteria for biological therapy, these patients will have failed to respond to or will have been intolerant to conventional systemic therapies (methotrexate and ciclosporin) thus limiting their further management options dramatically. In the absence of these relatively inexpensive treatment options, the GDG considered that the majority of these patients would rely on costly outpatient day care and very costly inpatient care to manage their disease. Based on recent resource utilisation studies from the UK and Netherlands and supported by their clinical experience, they outlined a much more resource intensive package of services likely to be used or required by people with moderate to severe psoriasis who did not have access to biological therapy. The GDG considered the results of the extensive sensitivity analyses around the cost of best supportive care. They considered that when best supportive care was less resource intensive (i.e. fewer annual hospitalisations, shorter length of stay and/or less outpatient day care),switching to a second biological drug was less likely to represent better value for NHS resources. Results showed that only when patients were assumed to have the worst baseline quality of life (and hence have the most to gain from successful treatment) would the substantial additional cost of delivering biological therapy compared to a less resource intensive best supportive care be offset. Conversely, if best supportive care was assumed to be more resource intensive than in the base case, then biological therapy was very likely to be most cost-effective, regardless of baseline quality of life. There was also uncertainty in the effectiveness of this newly defined best supportive care. Previous analyses have used the placebo response rates from the randomised controlled trials, which when used in the guideline model was virtually equivalent to assuming no response at all. This was varied upwards based on observational data from the UK which showed that response to inpatient treatment ranged between 65% and 83%. When inpatient treatment was assumed to be as effective as this, then the incremental cost-effectiveness ratio of switching to an alternative biological therapy increased to between

	£20,000 and £30,000 per QALY gained. Although quality of life gains are generally attached only to the clinical outcomes (i.e. PASI response), the GDG discussed whether gains might be affected by how the outcome was reached. They considered that although 3 weeks in hospital may induce an adequate level of response (PASI50), this could have a substantial negative impact on a patient's quality of life compared to a once or twice weekly injection or even an infusion every few months. Furthermore, in order to maintain that level of response, patients would likely have to carry on with regular outpatient day care appointments or use drug treatments that have failed in the past or have potentially serious adverse events (e.g. renal impairment or hepatotoxicity). The GDG recognised that the model included a population of patients with variable reasons for undergoing treatment with a second biological drug. This includes patients who may have been primary or secondary non-responders, patients who may have been intolerant to an initial biological or other reasons unrelated to the initial treatment. There is also no information about what biological therapy or therapies to which they may have been exposed. It is also unclear as to whether these patients have more or less severe disease than in trials of patients naïve to biological therapy. The GDG considered whether any of these patient differences were likely to impact the cost-effectiveness of biological therapy over best supportive care, and they concluded that the benefit over placebo was likely to be significant enough in any of these groups to justify the additional cost of biological therapy. This was especially true if the patient had very severe disease, as this group would have the most to gain from successful treatment. They noted too that the population likely to reach this point in the care pathway is very small (fewer than 1000 patients). They decided that switching to a second biological drug should be considered in all patients following failure of a first biological drug and noted that the same criteria as outlined in previous NICE guidance should be used to determine eligibility.
Quality of evidence	• Although in the protocol clear or nearly clear disease was defined as either minimal residual activity, PASI90 or clear or minimal on the PGA, the data showed that PASI90 and clear or minimal on the PGA were not equivalent outcomes, with PASI90 being a more stringent criterion for response. Therefore, both outcomes have been reported separately. • Most of the evidence is based on observational data and the GDG were mindful of the limitations of these studies, especially those that were not adjusted for confounders. The Ortonne study was the only one which was adjusted for confounders. • Not all studies state whether the first biological drug had been discontinued due to treatment failure or other reasons such as intolerance, loss to follow up and / or loss of funding for biological drug. • Some of the studies involved doses of biological drugs that are not NICE approved (usually double the NICE approved dose) with consequent risk of an under- or overestimate of benefit of a second

biological drug:

- The Mazzotta and Griffiths studies and the ACCEPT study used a dose greater than that approved by NICE of twice weekly 50mg dose of etanercept. When used at NICE approved doses (25mg twice weekly or 50mg weekly) the response rates are lower: therefore the benefit of a second biological drug in this study may be an overestimate.
- The Van study used 40mg weekly adalimumab. This is higher than the NICE approved dose (40mg every other week) and therefore response rates given in this study may overestimate those seen in UK practice.
- Some participants in the Menter study received 3 mg/kg infusions of infliximab, which is less than the NICE approved dose of 5 mg/kg and so the efficacy as a second biological drug may have been underestimated.
- Some participants were under- and some over-dosed in the ACCEPT, PHOENIX1 and PHOENIX-II trials as participants were randomised to 40 or 90 mg of ustekinumab regardless of their body mass index. Therefore, any under or overestimation of efficacy or toxicity should have balanced out, which was supported by subgroup data for only those receiving the licensed weight-based dosing showing no clear difference in results.

However, it is important to note that the dosing schedules of the prior biological drugs were not reported and if these were greater than the NICE approved doses the estimate of efficacy for the second biological drug may have been an under-estimate.

- The Mazzota study presented response rates for etanercept among those with and without concomitant psoriatic arthritis (PsA). However, there were some differences in the baseline characteristics of the subgroups. The PsA group were older, with more previous exposure to methotrexate and less severe skin disease. Therefore the GDG felt it was not possible to be certain whether a real difference exists between the two groups.
- The population in the Cassano study had a high prevalence of PsA and were assessed after just 12 weeks.
- The GDG noted the following limitations with the Menter study:
  - It was unclear which biological drug had been used first.
  - It was unclear whether the first biological drug had been stopped due to failure or for another reason.
- Infliximab as given in both 3 and 5 mg/kg dosages but the results were for these two groups were pooled. The Mazzotta, Ortonne, Cassano, Laws 2011, Griffiths 2010 studies were conducted in a European setting or had contributing centres in Europe, and therefore the GDG felt it was reasonable to assume that the first biological drug had been stopped due to failure.
- Some participants in the Ortonne study were receiving concomitant topical treatments. This reflects clinical practice. The data included adjusted and unadjusted figures.
- The Strober study did not state whether participants in the previous

	biological therapy group had also previously received systemic non-biological drugs. The study was conducted in the USA, so it is possible this group bypassed standard systemic non-biological treatment as US clinical practice differs from UK clinical practice. • There was evidence for the following sequences: o Etanercept > ustekinumab o Infliximab > adalimumab o Etanercept > adalimumab o Infliximab > etanercept • There was no evidence for the following sequences: o Adalimumab > etanercept o Adalimumab > ustekinumab o Ustekinumab > any TNF antagonist Overall: • There were four studies with randomised data available for subgroups with and without prior exposure to biological therapy: the comparisons were infliximab vs placebo (Menter); ustekinumab vs placebo (PHOENIX1 & 2); and ustekinumab vs etanercept (ACCEPT). The remaining studies were nonrandomised comparisons from RCTs or observational studies. • Some of the studies do not reflect clinical practice in terms of dosing and population. • The GDG had low or very low confidence in the evidence for a number of reasons. This included the short-term nature of the majority of studies, which is not representative of true practice for a chronic condition Only three studies gave data from 12 months (Phoenix 1 and 2 and Van). • There are some data to suggest a slightly better response in those with no prior exposure to biological therapy, however from the randomised data a second biological drug is clearly clinically more effective than placebo in people who have previously received a biological drug based on both relative and absolute differences in effect • In terms of PASI50 and change in DLQI there is no clinically significant difference in the response for those who have and have not previously received a prior biological drug in either relative or absolute terms. • There was no compelling evidence to suggest that switching from one particular biological drug to another particular biological drug is beneficial. The evidence is consistent with experience of GDG members. • Future research needed on cost and clinical effectiveness of
Other considerations	Both compartments (skin and joints) benefit from TNF antagonists; the GDG noted that at times, skin may have stopped responding to a biological drug whereas associated psoriatic arthritis remains well controlled. Any change in biological therapy should therefore be made

	in consultation with rheumatologists. The mechanisms underlying loss of response to biological drugs are poorly understood but may relate to development of drug antibodies. Identifying which people are likely to respond (or not) to biological drugs will be of patient and health economic benefit. The GDG noted that at present the existing Single Technology Appraisal guidance is variably interpreted by Primary Care Trusts, and consequently there is variation in access to second biological drugs across England and Wales. In areas where there is no access to second biological drugs, the GDG noted that resource is expended on trying to obtain funding (for example, clinician time completing paperwork). The GDG noted that children are not covered by the NICE technology appraisals for biological drugs. Etanercept is licensed for use in children.

1

14 Cognitive behavioural therapy

Psoriasis is a complex long-term condition that can make substantial physical and psychological demands on the patient[425]. Over a third of people with psoriasis report clinically significant anxiety and depression and levels of suicide ideation are increased in psoriasis. Less is known about actual suicide attempts.

Social embarrassment and rejection are common and this psychological and social impact results in reduced quality of life and lower levels of psychological well-being. The magnitude of impact on quality of life for people with psoriasis is thought to be similar to other long term conditions such as diabetes, cancer and cardio-vascular disease. Cross-sectional work has shown that distress affects clinical outcomes possibly through behavioural and biological pathways, reducing coping, impairing self-care and increasing non-adherence, this latter finding is particularly relevant to use of topical treatments in psoriasis. Furthermore, some studies suggest distress may actually trigger a psoriasis flare.

High levels of distress and poor coping are underpinned by a set of beliefs that are both general - about the person themselves, and their ability to manage a long-term condition, plus specific beliefs about the condition itself. These beliefs are useful predictors of self-management and form important targets for psychological treatment intervention designed to challenge and change them.

The NICE clinical guideline on depression[426] in adults includes recommendations on the use of cognitive behaviour therapy (CBT) for patients with low mood and depression and a long-term physical condition.

Access to psychological therapies has been, and continues to be, problematic as demand outstrips supply with many eligible patients waiting for long periods to access suitably trained therapists. Dedicated psychological service provision for patients with psoriasis only exists in highly specialised settings. More often, patients are referred to general mental health services and assessed according to standard mental illness criteria and therefore psoriasis specific issues may be missed. Patients are often reluctant to use mental health services partly due to the social embarrassment they experience living with psoriasis and partly because non-specialists do not understand or address key aspects of the condition sufficiently for them.

The GDG posed the following question: in people with psoriasis (all types), how effective are cognitive behavioural therapy (CBT) (group and individual) interventions for managing psychological aspects of the disease in reducing distress and improving quality of life?

14.1 Methodological introduction

A literature search was conducted for RCTs, systematic reviews or comparative observational studies that addressed the efficacy of cognitive behavioural therapy in people with psoriasis for managing the psychological aspects of the condition compared with standard care (the pharmacological intervention usually received by a person with psoriasis of a given severity and/or educational interventions). No time limit was placed on the literature search and there were no limitations on sample size or duration of follow-up. Indirect populations were excluded.

The outcomes considered were:

- Reduced distress, anxiety or depression (assed by change in Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI) or Speilberger State Trait Anxiety Inventory (STAI))
- Reduced stress (change in Psoriasis Life Stress Inventory [PLSI])
- Improved quality of life (change in Dermatology Life Quality Index [DLQI] or Psoriasis Disability Index [PDI])

- Reduced psoriasis severity (change in PASI)

One study[427], was found that addressed the question and was included in the review. Note that no studies were available that assessed cognitive behavioural therapy in an exclusively paediatric population.

The study design used patient-preference randomization and so was classified as a non-randomised controlled study. The intervention was a 6-session CBT programme delivered by medical, clinical psychology, and nursing personnel, called the Psoriasis Symptom Management Programme (PSMP), which lasted 2.5 hours. This consisted of didactic teaching about the medical and biological basis of psoriasis, stress-reduction techniques, cognitive techniques and homework in relation to individual perceptions as an adjunct to standard care. The comparison group received standard care, which included topical and systemic non-biological therapy.

14.1.2 Cognitive behavioural therapy vs. standard care

2 **Table 179: Evidence profile**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Standard care	Relative (95% CI)	Absolute	
PASI75 (follow-up 6 months)											
1 Fortune 2002B	observational studies[a]	very serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/28 (64.3%)	7/30 (23.3%)	RR 2.76 (1.36 to 5.58)	411 more per 1000 (from 84 more to 1000 more)	⊕OOO VERY LOW
Final PASI (follow-up 6 weeks; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[b]	no serious inconsistency	no serious indirectness	serious[c]	none	40	53	-	MD 1.9 lower (3.66 to 0.14 lower)	⊕OOO VERY LOW
Clinical Severity (PASI) (follow-up 6 months; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 2.0 lower[f]	⊕OOO VERY LOW
Disability (PDI) (follow-up 6 weeks; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[g]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 3.33 lower[h]	⊕OOO VERY LOW
Disability (PDI) (follow-up 6 months; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[g]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 3.05 lower[i]	⊕OOO VERY LOW

Depression (HADS) (follow-up 6 weeks; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 4.7 lower[j]	⊕OOO VERY LOW
Anxiety (HADS) (follow-up 6 weeks; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 2.8 lower[k]	⊕OOO VERY LOW
Depression (HADS) (follow-up 6 months; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 3.29 lower[h]	⊕OOO VERY LOW
Anxiety (HADS) (follow-up 6 months; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 2.92 lower[l]	⊕OOO VERY LOW
Stress (PLSI) (follow-up 6 weeks; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 3.9 lower[j]	⊕OOO VERY LOW
Stress (PLSI) (follow-up 6 months; Better indicated by lower values)											
1 Fortune 2002B	observational studies[a]	very serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	40	53	-	t-value 3.06 lower[m]	⊕OOO VERY LOW

(a) Patient-preference randomisation, no blinding, no allocation concealment
(b) High dropout rate and not matched for concomitant therapies
(c) Serious imprecision according to GDG discussion (confidence interval ranges from clinically important benefit to no clinically important benefit)
(d) Incomplete reporting, high dropout rate and not matched for concomitant therapies
(e) No measure of variance provided
(f) p=0.04
(g) Intervention and control not matched at baseline, incomplete reporting, high dropout rate and not matched for concomitant therapies
(h) p=0.001
(i) p=0.003

(j) p<0.001
(k) p=0.007
(l) p=0.004
(m) p=0.003

Although the t-values and p-values reported in the GRADE table were unadjusted for confounders, the study did report the results of repeated-measures ANCOVA with baseline scores included as covariates. This analysis was reported to show statistically significant effects of the intervention compared with standard treatment for PASI (p=0.001), anxiety (p=0.001), depression (p=0.001), psoriasis-related stress (p=0.001) and disability (p=0.04). However, it was not clear whether this was based on the 6 week or 6 month time-point or whether it was for a comparison of final or change scores.

The study did not report full details for the majority of outcomes, which were mainly presented graphically only. However, to aid clinical interpretation the available data are presented below to provide contextual information about the approximate magnitude of change in both groups relative to baseline values (see Table 180). Note that the study did not report mean scores as assessed by Psoriasis Disability Index or the depression scores from HADS.

Table 180: Clinical severity, anxiety and stress scores at baseline, 6 weeks and 6 months follow-up

Time point	PSMP	Standard care	p-value
Change in PASI (mean ± SD)			
Baseline	10.5 ± 2.7	9.2 ± 3.2	NS
6 weeks	6.5 ± 4.1	8.4 ± 4.5	0.03
6 months	6.5	8.0 ± 4.8	0.04
HADS (anxiety)			
Baseline	12	12	NS
6 weeks	8	11	0.007
6 months	8	11	0.004
PLSI (stress)			
Baseline	21	25	NS
6 weeks	15	24	<0.001
6 months	15	23	0.003

14.173 Evidence statements

In people with psoriasis, the cognitive behavioural therapy group had a significantly lower mean score than standard care (P<0.05) for:

- PASI75 at 6 months [1 study; 58 participants; very low quality evidence][427]
- Final PASI at 6 weeks [1 study; 93 participants; very low quality evidence][427]
- Clinical severity as measured by PASI at 6 months [1 study; 93 participants; very low quality evidence][427]
- Disability as measured by PDI at 6 weeks and 6 months [1 study; 93 participants; very low quality evidence][427]
- Depression as measured by HADS at 6 weeks and 6 months [1 study; 93 participants; very low quality evidence][427]
- Anxiety as measured by HADS at 6 weeks and 6 months [1 study; 93 participants; very low quality evidence][427]
- Stress as measured by PLSI at 6 weeks and 6 months [1 study; 93 participants; very low quality evidence][427]

14.174 Economic evidence

No relevant economic evidence was identified.

14.175 Linking evidence to recommendations

Recommendations	No recommendations.
Future research recommendations	**26.In people with psoriasis being treated with systemic non-biological**

	or biological therapies what clinical or other markers prevent optimal treatment outcomes? **27. In people with psoriasis, does early intervention to achieve and maintain complete disease remission alter the long term prognosis in terms of psoriasis severity , co-morbidities, or treatment related adverse effects and are there any clinical or other biomarkers that can be used to identify those most likely to benefit from this treatment approach?**
Relative values of different outcomes	The following outcomes were considered by the GDG and given equal weight: • Reduced distress / anxiety / depression • Reduced stress • Improved quality of life • Reduced psoriasis severity
Trade off between clinical benefits and harms	There was only one small UK CBT study that was situation specific to people with psoriasis. The GDG had low confidence in the study results, all outcomes were considered to be of low or very low quality. Given this the GDG made a future research recommendation.
Economic considerations	No economic evidence was available to inform the GDG on the cost-effectiveness of cognitive behavioural therapy in the management of patients with psoriasis. The GDG discussed the significant psychological impact psoriasis can have on patients' quality of life and generally believed that CBT or other psychological interventions may help some patients; however, on the basis of inconclusive clinical evidence, they could not be sure that this would represent good value for NHS resources. They felt that further research was warranted in order to measure clinical and quality of life benefits associated with psychological interventions and also to better identify patients who might gain the most from such interventions.
Quality of evidence	• Paucity of data - only one study (Fortune 2002B). • The Fortune study was patient preference design. This means participants were given the choice as to which arm of the study to enter. This method is often used in psychological trails to reduce drop outs. All participants were given CBT sessions at the same site with the same people delivering CBT. • The GDG noted the following issues with the quality of the study: o The groups were not matched at baseline for disability scores o There were substantial drop outs in both groups o There were differences in the prescribed treatments, which potentially may confound some of the results o Incomplete reporting (actual changes scores were not reported for some scales) o Very low quality evidence rating for all outcomes • The GDG noted that CBT improved HADS score and distress, but felt the improvement in PASI was unconvincing.

	• More people in the CBT group converted from topicals to systemic therapies. The proportions did not change much in the standard care group. Therefore improvement in PASI could be due to changes in treatment. The GDG acknowledged that moving to systemic treatment could explain the improved PASI, but this does not mean that CBT has not helped. • There appeared to be a discrepancy between the small difference in final PASI and the clinically significant improvement in the numbers achieving PASI75 in the CBT group. It was discussed that this may be explained by a high percentage of people achieving 71-74% improvement in the control group and being classified as not achieving PASI75; alternatively it may be due to the difference in baseline PASI between the two groups (1.3 points higher in the CBT group). • The GDG did not wish to make a national recommendation due to the lack of evidence. • The GDG agreed to make future research recommendations on whether CBT is of value and identifying which individuals are most likely to benefit from CBT. Future research should take into account disease severity which should be controlled at baseline.
Other considerations	• The GDG discussed whether it is possible to separate the impact of the educational component from other aspects of CBT. The GDG were aware that in cardiovascular disease and diabetes, it is known that an educational component is not enough to manage psychological distress and poor coping. Although educational strategies will help alleviate distress, a clinical effect may not be achieved without a cognitive-behavioural element. The separate effects of education and CBT are unknown for psoriasis. • The GDG discussed whether improvement in anxiety and depression may help self-management, or vice versa. The GDG were aware of research work investigating whether managing depression dampens the psoriasis inflammatory response.

15 Glossary and abbreviations

15.1 Glossary

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acrodermatitis of Halopeau	Redness, scaling that commences in and around the nails and nail beds of the fingers and toes progressing to nail dystrophy and paronychial, periungal swelling and deformity
Adequate response	A response of either a reduction of at least 50% on the PASI plus a decrease in DLQI of 5 points or more, or a reduction of at least 75% on the PASI.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clear or nearly clear	Response at a score of 0 or 1 on the Physician's Global Assessment
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.

Term	Definition
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).

Term	Definition
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Difficult-to-treat sites	Encompasses the face, flexures, genitalia, scalp, palms and soles
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Erythroderma	Confluent psoriasis involving more than 90% of the skin surface area
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
First line therapy	Traditional topical therapies including corticosteroids, vitamin D and analogues, dithranol and tar preparations
Fitzpatrick scale	The Fitzpatrick scale is a physician-diagnosed skin phototype (PSPT) and relies on the visual assessment of pigmentation as an indicator of skin responses to sunlight. I, always burn/never tan; II, usually burn/tan with difficulty; III, sometimes burn/usually tan; IV, rarely burn/tan easily; V, darker skin; VI, darkest skin
Fitzpatrick skin type I	White; very fair; freckles; typical albino skin.

Term	Definition
	Always burns, never tans
Fitzpatrick skin type II	White; fair. Usually burns, tans with difficulty
Fitzpatrick skin type III	Beige; very common. Sometimes mild burn, gradually tans to a light brown
Fitzpatrick skin type IV	Beige with a brown tint; typical Mediterranean Caucasian skin. Rarely burns, tans with ease to a moderate brown.
Fitzpatrick skin type V	Dark brown. Very rarely burns, tans very easily
Fitzpatrick skin type VI	Black. Never burns, tans very easily, deeply pigmented.
Flexural sites	May include any or all of the following areas: axilla, groin, submammary folds, natal cleft and genitals
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Generalised pustular psoriasis	Sheets of small, monomorphic pustules often involving the edges of expanding, intensely inflammatory plaques or developing within erythrodermic skin. Associated with constitutional upset (eg: fever, malaise)/. May be preceded by plaque psoriasis or arise de novo
Generalist care (Level 2)	People with skin conditions needing generalist (Level 2; primary care) care are managed initially through self-referral to their GP. Level 2 care should also include access to input from suitably trained nurses.
Gold standard See 'Reference standard'.	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Guttate psoriasis	An acute eruption of small (< 1 cm) papules of psoriasis which typically appear over a period of 1 month, persist for a month, and usually resolve during the third month. Lesions most commonly occur on the trunk, i.e. a centripetal distribution
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity Or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such

Term	Definition
	results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inadequate response	A response of less than 50% reduction in the PASI score and a decrease in DLQI of less than 5 points, and/or less than 75% reduction in the PASI score.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Localised pustular psoriasis	Includes palmoplantar pustulosis and acrodermatitis of Halopeau
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to

Term	Definition
	produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
Palmoplantar pustulosis	Chronic, pustular eruption typically involving the palms and soles with crops of yellow, sterile pustules
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Phototherapy	Includes both PUVA, BBUVB and NBUVB
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Plaque-type psoriasis	Characterized by red, scaly, discoid lesions varying in size from 0.5 cm in diameter to large confluent areas. May occur as single lesions at predisposed sites (e.g. extensor aspects of knees and elbows) or disseminated (generalized) over the body.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	For diagnostic tests. The proportion of patients with that particular test result who have the target disorder (post test odds/[1 + post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may

Term	Definition
	depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Psoriasis	Refers to plaque-type psoriasis unless otherwise specified
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Rapid relapse	Greater than 50% of baseline disease severity within 3 months of stopping treatment.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear

Term	Definition
	slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Satisfactory response	A response to treatment that is judged to be satisfactory by both the person with psoriasis and the clinician.
Sebo-psoriasis	Thin, red and well-demarcated plaques with variable degrees of scaling at nasolabial folds medial cheeks, nose, ears, eyebrows, scalp, presternal and interscapular regions (may occur with plaque psoriasis)
Second line therapy	Phototherapy and non-biological systemic agents
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Self-care (Level 1)	People with skin conditions who manage their conditions themselves (Level 1 care) should be supported with high-quality patient information and input from suitably trained nurses, patient support groups and community pharmacists People with skin conditions needing generalist (Level 2) care are managed initially through self-referral to their GP. Level 2 care should also include access to input from suitably trained nurses. Any patient whose skin condition cannot be managed by a generalist will need to be referred for specialist care (Level 3) and/or supra-specialist services (Level 4).
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more

Term	Definition
	parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specialist and supra-specialist care (Level 3)	Any patient whose skin condition cannot be managed by a generalist will need to be referred for specialist care (Level 3) and/or supra-specialist services (Level 4). This is secondary and tertiary care.
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Third line therapy	Systemic biological therapies such as the TNF antagonists adalimumab, etanercept and infliximab, and ustekinumab, an anti-IL12-23 monoclonal antibody
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Unsatisfactory response	A response to treatment that is judged to be unsatisfactory by both the person with psoriasis and the clinician.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Vitamin D and analogues	This includes the naturally occurring active metabolite of vitamin D, calcitriol (1α25-dihydroxyvitamin D3 and two synthetic vitamin D analogues, calcipotriol and tacalcitol (1α24-dihydroxyvitamin D3)
Wellbeing	A general term that encompasses both quality of life and mood or distress

15.2 Abbreviations

2

Abbreviation	Definition
ALT	Alanine transaminase

AP	Alkaline phosphatase
APRI	Aspartate transaminase to platelet ratio index
AST	Aspartate transaminase
BBUVB	Broadband ultraviolet B
BDI	Beck Depression Inventory
BMI	Body Mass Index
BNF	British National Formulary
CASPAR	Classification Criteria for Psoriatic Arthritis
CBT	Cognitive behavioural therapy
c-GT	c-glutamyl transpeptidase
CRP	C-reactive protein
CSA	Ciclosporin
CTCL	Cutaneous T-cell lymphoma
CVD	Cardiovascular disease
DLQI	Dermatology Life Quality Index
DMARD	Disease modifying anti-rheumatic drug
ELF	Enhanced liver fibrosis
ESR	Erythrocyte sedimentation rate
GGT	Gamma-glutamyl tranferase
GPRD	General Practice Research Database
HA	Hyaluronic acid
HADS questionnaire	Hospital Anxiety and Depression questionnaire
HAQ	Health Assessment Questionnaire
IRR	Incidence rate ratio
LDH	Lactate dehydrogenase
MI	Myocardial infarction
MM	Malignant melanoma
MTX	Methotrexate
NBUVB	Narrowband ultraviolet B
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PGA	Physician's Global Assessment
PIIINP	Procollagen-3 N-terminal peptide
PLSI	Psoriasis Life Stress Inventory
PT	Prothrombin time
PUVA	Psoralen plus ultraviolet A
SCC	Squamous cell carcinoma
SIR	Standardised incidence rate
SMR	Standardised morbidity ratio
SPC	Summary of Product Characteristics
STAI	Speilberger State Trait Anxiety Inventory
TIMP-1	Tissue inhibitor of metalloproteinase 1

TNF antagonists	Tumour necrosis factor antagonist
VTE	Venous thromboembolism

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Appendices (see separate files):

Appendix A: Scope

Appendix B: Declarations of interest

Appendix C: Review protocols

Appendix D: Literature search strategies

Appendix E: Study selection flow charts

Appendix F: Excluded studies list (clinical)

Appendix G: Excluded studies list (cost effectiveness)

Appendix H: Evidence tables – clinical studies

Appendix I: Evidence tables – economic studies

Appendix J: Forest plots

Appendix K: NMA topicals trunk and limbs

Appendix L: NMA topicals scalp

Appendix M: CEA topicals trunk and limbs

Appendix N: CEA topicals scalp

Appendix O: CEA 2nd line biologics

Appendix P: Review to define 'best supportive care'

Appendix Q: Additional data (appendices from evidence reports)

Appendix R: Research recommendations

Appendix S: Information to facilitate discussion of risks and benefits of treatments for people with psoriasis