Appendix C: Review protocols

C.1 Assessment

C.1.1 Tools for assessing disease severity and impact

Component	Description
Review 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?
Objectives	The aim of this review is to compare the validity of available tools (psoriasis-specific or dermatology-specific but validated in psoriasis) to assess the severity and impact of psoriasis in all people with the disease, including at first presentation and follow-up visits.
Population	All people with psoriasis
Subgroups	The following groups will be considered separately if data are present: • People with psoriasis at high impact or difficult to treat sites • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis
Intervention	Severity: PASI, target plaque scores, SPI, BSA, SAPASI, PGA, LS-PGA, Copenhagen psoriasis severity index, photography, GSS, PSSI, s-mPASI, HN-PASI, S-PaGA, NAPSI Impact: DLQI, CDLQI, Skindex-17 or -29, scalpdex, Dermatology Quality of Life scales, The Dermatology Specific Quality of Life Instrument, Impact of Psoriasis Questionnaire, PSORIQoL, PQoL-12, SPI, PDI, PLSI, Questionnaire on Experience with Skin Complaints
Comparison	As above
Outcomes	• Construct validity – convergent and divergent • Inter-rater reliability • Intra-rater reliability • Internal consistency • Repeatability • Practicability • Sensitivity to change
Study design	Validity and reliability studies or systematic reviews
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using domains relevant for validity and reliability studies as no NICE checklists are available. Synthesis of data

	• Data will be presented in tabular format with narrative summary.

C.1.2 Diagnostic tools for Psoriatic Arthritis

Component	Description
Review question	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?
Objectives	The aim of this review is to determine what is the most accurate tool for use in people with psoriasis in non-rheumatological settings to identify those with likely psoriatic arthritis to prompt referral
Population	All people with psoriasis
Subgroups	The following groups will be considered separately if data are present: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis
Intervention	• Psoriatic Arthritis Screening and Evaluation Tool (PASE) • Psoriasis Epidemiology Screening Tool (PEST) • Toronto Psoriatic Arthritis Screen (ToPAS) • Psoriatic Arthritis Questionnaire (PAQ) • Modified PAQ (mPAQ)
Comparison	• Classification Criteria for Psoriatic Arthritis (CASPAR), • Moll and Wright criteria • Standard clinical diagnosis
Outcomes	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio
Study design	Diagnostic cohort or case-control studies
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate.

C.1.3 Specialist referral for Psoriatic Arthritis

Component	Description
Review 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?
Objectives	The aim of this review is to estimate the impact of timing of referral to a specialist on the outcomes of people with psoriasis who have suspected psoriatic arthritis
Population	All people with psoriasis and suspected psoriatic arthritis
Subgroups	The following groups will be considered separately if data are present: • Children • Polyarthritis at presentation • Different psoriasis severities • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Site of psoriasis
Prognostic factors	• Timing of referral
Outcomes	• Quality of life : HAQ, EQ5D • Disease symptoms/signs: Pain, tenderness, joint swelling (or second-line therapy as a surrogate) • Joint damage: Clinical (e.g. joint damage), radiological (e.g. Sharp, Larsen, Steinbrocker) • Biochemical markers : CRP and ESR • Mortality • Cardiovascular events
Study design	Prospective observational studies
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists Synthesis of data • Meta-analysis will be conducted where appropriate. • Effect estimates, with their 95% confidence intervals, will be extracted from the papers.

C.1.4 Identification of comorbidities

Component	Description
Review question	Are people with psoriasis at higher risk than people without psoriasis for significant comorbidities and are there subgroups within the psoriasis population at a further increased risk?
Objectives	The aim of this review is to compare the incidence of specific comorbidities in people with psoriasis (all types) with the prevalence in the general population and to determine whether there are subgroups within the psoriasis population at a further

	increased risk.
Population	All people with psoriasis
Prognostic factors	• Psoriasis
Subgroups for prognosis	The following prognostic factors will be considered for subgroup analysis if data are present: • Children • Severity of psoriasis (mild vs severe; may be indicated by hospital admission/treatment in secondary care) • Treatments used (e.g., phototherapy/immunosuppressive drug use – including biological therapies) • Lifestyle markers (smoking, alcohol)
Outcomes	Incidence of the following comorbidities: • Obesity • Cardiovascular disease (including stroke) • Alcohol-related disease • Cancer (skin cancer, lymphoma, or overall cancer risk) • Liver disease (especially NASH/NAFLD) • Diabetes mellitus • Hypertension • Depression • Inflammatory bowel disease
Study design	• Systematic reviews • RCTs • Cohort studies • Case-control studies • Case series (with a suitable comparator group)
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists Synthesis of data • Meta-analysis will be conducted where appropriate • Effect estimates, with their 95% confidence intervals, will be extracted from the papers.

C.1.5 Phototherapy, systemic therapy, tar and risk of skin cancer

Component	Description
Review question	In people with psoriasis (all types) who have been exposed to coal tar, phototherapy (BBUVB, NBUVB and PUVA), systemic non-biological or biological therapy, what is the risk of skin cancer compared with people not exposed to these interventions and which individuals are at particular risk?

Objectives	The aim of this review is to determine the risk of skin cancer in people who have been exposed to coal tar, phototherapy or systemic non-biological or biological therapy compared to an unexposed cohort and to establish whether there are particular subgroups of the population at higher risk.
Population	All people with psoriasis who have been exposed to coal tar, phototherapy (BB-UVB, NBUVB and PUVA), systemic non-biological or biological therapy
Prognostic factors	• NB-UVB • BB-UVB • PUVA • Methotrexate • Ciclosporin • Acitretin • Biological therapies (adalimumab, infliximab, etanercept, ustekinumab) • Coal tar
Subgroups for prognosis	The following prognostic factors will be considered for subgroup analysis if data are present: • Children • Fair skin (Fitzpatrick phototype 1-3) • Smoking status • Alcohol consumption status • Concomitant or previous immunosuppressive treatments • Duration of previous systemic treatment • Disease severity • Previous skin cancer • Cumulative exposure to previous treatment (phototherapy [BB-UVB, NBUVB and PUVA – systemic and topical] or systemic non-biological or biological therapy or coal tar) • Family history of skin cancer • Age at first exposure
Outcomes	Incidence of the following comorbidities: • Melanoma skin cancer • Non melanoma skin cancer – stratified as squamous cell carcinoma and basal cell carcinoma if data are available
Study design	• Systematic reviews • RCTs • Cohort studies
Population size and directness	• At least 10 events per covariate (for accurate multivariate analysis to be possible) • Studies with indirect populations will not be considered • Follow-up >12 months (as cancer does not develop immediately)
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists Synthesis of data • Meta-analysis will be conducted where appropriate

	• Effect estimates, with their 95% confidence intervals, will be extracted from the papers.

C.2 Topical therapies for chronic plaque psoriasis

C.2.1 Topical therapies for trunk and limb chronic plaque psoriasis

Component	Description
Review question	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 or vitamin D analogues, potent or very potent corticosteroids, tar, dithranol and retinoids compared with placebo or vitamin D or vitamin D analogues, and of combined or concurrent vitamin D analogues and potent corticosteroids compared with potent corticosteroid or vitamin D or vitamin D analogue alone?
Objectives	The aims of this review are to assess the clinical and cost-effectiveness and safety of topical vitamin D or vitamin D analogues, potent or very potent corticosteroids, tar, dithranol and retinoids for the trunk and/or limbs compared with placebo and with vitamin D or vitamin D analogues, as well as combined/concurrent vitamin D or vitamin D analogues compared with potent corticosteroid or vitamin D or vitamin D analogue alone; and to establish the period of time that topical therapies should be administered for before efficacy is reviewed and the patient is moved on to alternative therapy if topicals are ineffective.
Population	All people with chronic plaque psoriasis of the trunk and/or limbs
Subgroups	The following groups will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis The following factors will be considered for subgroup analysis if heterogeneity is present: • Duration of treatment • Individual agents within the vitamin D or vitamin D analogue and corticosteroid classes • Within- and between-patient randomisation • Disease severity • Formulation • Dose • Skin type/ethnicity • Psoriatic arthritis
Intervention	• Vitamin D or vitamin D analogues (calcipotriol/calcipotriene [Dovonex], calcitriol [Silkis], tacalcitol [Curatoderm]), • Potent corticosteroids (betamethasone dipropionate [Betnovate-RD], betamethasone valerate [Betacap, Betesil, Bettamousse, Betnovate, Cutivate, Diprosone, Elocon], budesonide, fluticasone propionate [Cutivate], mometasone furoate [Elocon], fluocinolone acetonide [Synalar], beclomethasone dipropionate, triamcinolone acetonide, hydrocortisone butyrate [Locoid, Locoid Crelo, Metosyn, Nerisone, Synalar]) • Very potent corticosteroids (clobetasol propionate [Clarelux, Dermovate], diflucortolone valerate [Nerisone]), • Combined (combined product containing calcipotriol monohydrate and betamethasone dipropionate) or concurrent vitamin D or vitamin D analogue and

	potent corticosteroid (one applied in the morning and one in the evening) • Tar (Carbo-Dome, Cocois, Exorex, Psoriderm, Sebco, Coal Tar Solution, BP Pinetarsol, Polytar, Emollient, Psoriderm); • Dithranol (Dithrocream, Micanol, Psorin); • Retinoids (tazarotene [Zorac]) Note: only UK licensed interventions will be considered
Comparison	For all monotherapies: • Vitamin D or vitamin D analogues or placebo/vehicle For combined/concurrent vitamin D or vitamin D analogues and potent corticosteroid: • Potent corticosteroid or vitamin D or vitamin D analogues alone
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) • 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
Study design	RCTs or systematic reviews
Population size and directness	• Sample size greater than 25 per arm • Efficacy data to be reported for the primary end point of the trial if multiple time points are reported • No restrictions on treatment duration • Studies with indirect populations will not be considered • Studies only comparing different dosages or formulations of the same intervention will not be included • Studies comparing interventions within the classes of either vitamin D or vitamin D analogues or corticosteroids will not be included (unless the comparison is for frequency of administration e.g., once or twice daily dosing) • Studies assessing the whole body (including scalp, flexures and face), that do not stratify results by site of involvement will be included in this review.
Setting	• Primary care. • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Data on all vitamin D or vitamin D analogues will be pooled into one analysis as will data on any potent corticosteroids and on very potent corticosteroids

	The following information will also be recorded: • Who is administering the treatment (patient or HCP) • Number of applications/quantity of topical used • Setting • Formulation

C.2.2 Topical therapies for high impact or difficult to treat sites

Component	Description
Review question	In people with chronic plaque 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 or 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?
Objectives	The aims of this review are to assess the clinical and cost-effectiveness and safety of available topical therapies for chronic plaque psoriasis at high impact or difficult-to-treat sites (scalp, flexures, face); and to establish the period of time that topical therapies should be administered for at these sites before efficacy is reviewed and the patient is moved on to alternative therapy if topicals are ineffective.
Population	All people with chronic plaque psoriasis at high impact or difficult-to-treat sites (scalp, flexures, face)
Subgroups	The following groups will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis The following factors will be considered for subgroup analysis if heterogeneity is present: • Duration of treatment • Individual agents within the vitamin D or vitamin D analogue and corticosteroid classes • Within- and between-patient randomisation • Disease severity • Formulation • Dose • Skin type/ethnicity • Psoriatic arthritis
Intervention	• Vitamin D or vitamin D analogues (calcipotriol/calcipotriene [Dovonex], calcitriol [Silkis], tacalcitol [Curatoderm]) • Mild to very potent corticosteroids (hydrocortisone [Dioderm, Mildison, Synalar], clobetasone butyrate [Eumovate], fludroxycortide [Haelan], alclometasone dipropionate [Modrasone], fluocortolone [Ultralanum Plain], betamethasone dipropionate [Betnovate-RD], betamethasone valerate [Betacap, Betesil, Bettamousse, Betnovate, Cutivate, Diprosone, Elocon], budesonide, fluticasone propionate [Cutivate], mometasone furoate [Elocon], fluocinolone acetonide [Synalar], beclomethasone dipropionate, triamcinolone acetonide, hydrocortisone butyrate [Locoid, Locoid Crelo, Metosyn, Nerisone, Synalar], clobetasol propionate [Clarelux, Dermovate, Etrivex], diflucortolone valerate [Nerisone]) • Combined [combined product containing calcipotriol monohydrate and betamethasone dipropionate, Xamiol] or concurrent vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening) • Pimecrolimus [Elidel]

	• Tacrolimus [Protopic] • Tar [Carbo-Dome, Cocois, Exorex, Psoriderm, Sebco, Coal Tar Solution, BP Pinetarsol, Polytar, Emollient, Psoriderm] • Dithranol [Dithrocream, Micanol, Psorin] • Retinoids (tazarotene [Zorac])
Comparison	• Placebo/vehicle • Corticosteroids • Vitamin D or vitamin D analogues
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) • 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
Study design	RCTs or systematic reviews
Population size and directness	• Sample size greater than 25 per arm • Efficacy data to be reported for the primary end point of the trial if multiple time points are reported • No restrictions on treatment duration • Studies with indirect populations will not be considered • Studies only comparing different dosages or formulations of the same intervention will not be included • Studies comparing interventions within the classes of either vitamin D or vitamin D analogues or corticosteroids will not be included (unless the comparison is for frequency of administration e.g., once or twice daily dosing) • Studies assessing the whole body (including scalp, flexures and face), that do not stratify results by site of involvement will be included in this review.
Setting	• Primary care. • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Data on all vitamin D or vitamin D analogues will be pooled into one analysis as will data on any potent corticosteroids and on very potent corticosteroids The following information will also be recorded:

	• Who is administering the treatment (patient or HCP) • Number of applications/quantity of topical used • Setting • Formulation

C.3 Phototherapy

C.3.1 Phototherapy

Component	Description
Review question	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?
Objectives	The aim of this review is to asses the clinical- and cost-effectiveness and safety of the different phototherapies used as monotherapy compared with each other and with placebo or no treatment.
Population	All people with psoriasis
Subgroups	The following groups/interventions will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Bath and oral PUVA • Hand and foot PUVA • Psoriatic arthritis The following factors will be considered for subgroup analysis if heterogeneity is present: • Treatment frequency • Skin type (I-II vs III-VI) • Ethnicity • Disease severity • Between vs within-patient randomisation
Intervention	• BB-UVB • NBUVB • PUVA (bath or oral administration of psoralen)
Comparison	• Placebo/no treatment • BB-UVB • NBUVB • PUVA (bath or oral administration of psoralen)
Outcomes	• 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 (or number of treatments) to remission/max response • Change in DLQI • Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved) • Cataracts
Study design	RCTs or systematic reviews

Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate Additional data recorded • Home vs hospital setting • Different numbers of a phototherapy treatment per week • PUVA vs UVA + placebo

C.3.2 Phototherapy combined with acitretin

Component	Description
Review 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?
Objectives	The aim of this review is to asses the clinical and cost-effectiveness and safety of NBUVB and PUVA combined with acitretin compared with each other and with acitretin, UVB and PUVA as monotherapies.
Population	All people with psoriasis
Subgroups	The following groups/interventions will be considered separately if data are available: • Children • Narrowband and broadband UVB • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Bath and oral PUVA • Hand and foot PUVA • Psoriatic arthritis The following factors will be considered for subgroup analysis if heterogeneity is present: • Treatment frequency • Skin type (I-II vs III-VI) • Ethnicity • Disease severity • Between vs within-patient randomisation
Intervention	• Acitretin + UVB (re-UVB) • Acitretin + PUVA (re-PUVA) Note: only consider bath and oral administration of psoralen for PUVA will be considered and etretinate is not included

Comparison	• Acitretin • UVB • PUVA • re-NBUVB • re-PUVA
Outcomes	• PASI75 • PASI50 • Change in PASI (mean improvement) • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA) • Time-to-relapse • Relapse (time-to-event data if available otherwise ordinal data accepted) • 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)
Study design	RCTs or systematic reviews
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate

C.3.3 Dithranol, coal tar and vitamin D or vitamin D analogues combined with UVB

Component	Description
Review question	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 or vitamin D analogues compared with UVB alone or topical therapy alone?
Objectives	The aim of this review is to assess the clinical and cost-effectiveness and safety of UVB used in combination with topical therapies compared with UVB or topical monotherapies.
Population	All people with psoriasis
Subgroups	The following groups/interventions will be considered separately if data are available: • Children • Narrowband and broadband UVB • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Bath and oral PUVA • Hand and foot PUVA • Psoriatic arthritis

	The following factors will be considered for subgroup analysis if heterogeneity is present: • Treatment frequency • Skin type (I-II vs III-VI) • Ethnicity • Disease severity • Between vs within-patient randomisation
Intervention	• UVB + dithranol, • UVB + coal tar • UVB + calcipotriol, calcitriol or tacalcitol
Comparison	• UVB • Dithranol • Coal tar • Calcipotriol, calcitriol or tacalcitol
Outcomes	• 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 • Burn (grade 3 erythema or grade 2 erythema with >50% BSA involved) • Cataracts Number of UV treatments (as a surrogate for cumulative dose)
Study design	RCTs or systematic reviews
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate

C.4 Systemic therapy (second-line, non-biological)

Component	Description
Review question	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?
Objectives	The aim of this review is to asses the clinical and cost-effectiveness and safety of systemic methotrexate, cyclosporine and acitretin compared with each other and with placebo or no treatment.

Population	All people with psoriasis
Subgroups	The following groups will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Psoriatic arthritis The following factors will be considered for subgroup analysis if heterogeneity is present: • Intervention dose • Frequency of administration • Disease severity • Skin type and ethnicity
Intervention	• Methotrexate, • Cyclosporine • Acitretin
Comparison	• Placebo • Methotrexate, • Cyclosporine • Acitretin
Outcomes	• PASI75 • PASI50 • Change in PASI (mean improvement) • Clear or nearly clear (minimal residual activity/PASI>90/0 or 1 on PGA) • Improvement (for PPP) • Relapse (time-to-event data if available otherwise ordinal data accepted) • Time to remission/max response • Change in DLQI • Severe adverse events • For MTX: hepatotoxicity, marrow suppression and pneumonitis • For acitretin: hyperlipidaemia, hepatotoxicity, skeletal AEs and cheilitis • For CSA: renal impairment, hypertension, gout and hyperuricaemia • Withdrawal due to toxicity
Study design	RCTs or systematic reviews Cohort or case-control studies for long-term safety data
Population size and directness	• Sample size >10 • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate

C.5 Methotrexate and risk of hepatotoxicity

Component	Description
Review question	In people with psoriasis (all types) who are being treated with methotrexate, are there specific groups who are at high risk of hepatotoxicity?
Objectives	The aim of this review is to compare the prevalence of hepatotoxicity among specific patient groups while taking methotrexate to determine whether they are at a particular risk of this complication.
Population	All people with psoriasis being treated or considered for treatment with methotrexate
Subgroups	The following groups will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis
Prognostic factors	• Metabolic syndrome • Diabetes • Obesity • Hypertension • Hypercholesteroleamia • Alcohol • Liver disease • Hepatitis B or C • Pre-existing liver disease • Infectious hepatitis
Outcomes	• Biopsy grade • Biopsy grade progression • Periportal inflammation • Fatty change • Fibrosis • Cirrhosis • Abnormal liver function tests
Study design	Systematic reviews, cohort studies, case-control studies and case series
Population size and directness	• Sample size ≥30 • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists. Synthesis of data • Meta-analysis will be conducted where appropriate • Effect estimates, with their 95% confidence intervals, will be extracted from the papers.

C.6 Methotrexate and monitoring for hepatotoxicity

Component	Description

Review question	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?
Objectives	The aim of this review is to determine the most accurate method of monitoring for liver damage in people with psoriasis who are being treated with or about to begin treatment with MTX.
Population	All people with psoriasis being treated/referred for treatment with methotrexate
Subgroups	The following groups will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Psoriatic arthritis
Intervention	• Imaging techniques - liver ultrasound, liver scintigraphy, ultrasound elastography (achieved using the FibroScanR) • serum markers: serial pro-collagen III, 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 (ALP), aspartate aminotransferase (AST), total bilirubin, albumin, total protein, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT) and prothrombin time (PT))
Comparison	• Liver biopsy
Outcomes	• Specificity • Sensitivity • Negative predictive value • Positive predictive value • Positive likelihood ratio • Negative likelihood ratio
Study design	Diagnostic cohorts and case-control studies
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate.

C.7 Sequencing of biological therapy

Component	Description
Review question	In people with chronic plaque psoriasis eligible to receive biological therapy, if the first biological agent fails, which is the next effective, safe and cost effective strategy?
Objectives	The aim of this review is to asses the clinical and cost-effectiveness and safety of etanercept, infliximab, adalimumab and ustekinumab in people with chronic plaque psoriasis who have already received one biological agent.
Population	All people with chronic plaque psoriasis
Subgroups	The following groups will be considered separately if data are available: • Children
Intervention	• Second line etanercept, infliximab, adalimumab or ustekinumab
Comparison	• Etanercept, infliximab, adalimumab, ustekinumab (first-line or second line), methotrexate, ciclosporin, acitretin, placebo
Outcomes	• 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 • Severe adverse events • Withdrawal due to toxicity
Study design	Systematic reviews, RCTs, comparative observational trials
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate

C.8 Cognitive behavioural therapy

Component	Description
Review question	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?

Objectives	The aim of this review is to establish the clinical and cost effectiveness of CBT interventions for managing psychological aspects of psoriasis in order to reduce stress and improve quality of life.
Population	All people with psoriasis
Subgroups	The following groups will be considered separately if data are available: • Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Psoriatic arthritis
Intervention	• Psychological management (CBT – group and individual) in addition to or instead of standard care
Comparison	• Standard care alone (the pharmacological intervention usually received by a person with psoriasis of a given severity and/or educational interventions)
Outcomes	• 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)
Study design	Systematic reviews and RCTs; if no RCTs are available cohort studies and case-control studies will be sought
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered. • Any treatment duration with at least 6-months post-psychological intervention follow-up will be considered
Setting	• Primary • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate

C.9 Self-management

Component	Description
Review question	What strategies can best support people with psoriasis (all types) to self-manage the condition effectively?
Objectives	The aim of this review is to establish the best way to provide support to people with psoriasis to allow effective self-management of the condition.
Population	All people with psoriasis
Subgroups	The following groups will be considered separately if data are available:

	• Children • Different psoriasis phenotypes – e.g., pustular, erythrodermic, plaque, guttate, flexural or sebopsoriasis • Psoriatic arthritis
Intervention	• Self-management support (including for example education packages, interactive programmes, access to nurse specialist)
Comparison	• As above or standard care alone (the pharmacological intervention usually received by a person with psoriasis of a given severity and/or educational interventions)
Outcomes	• 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
Study design	Systematic reviews and RCTs; if no RCTs are available cohort studies and case-control studies will be sought (before and after comparisons would be excluded)
Population size and directness	• No limitations on sample size. • Studies with indirect populations will not be considered (note that this non-pharmacological intervention is not thought to act differently among different dermatological conditions, although the psychological stresses and impact on quality of life associated with psoriasis may be unique; therefore, a population cut-off of at least 40% psoriasis was decided upon)
Setting	• Primary • Secondary care • Tertiary care • Community settings in which NHS care is received.
Search Strategy	See appendix D
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate

C.10 Health economics literature review protocol

Health economics literature review protocol	
Objectives	The aim is to identify economic studies relevant to the review questions for the guideline set out above
Criteria	Populations, interventions and comparators as specified in the review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis)
Search strategy	See appendix D, section D.4
Review strategy	Study assessment: • NICE economic evaluation checklist{National Institute for Health and Clinical Excellence, 2009 NICE2009C /id}

Inclusion/exclusion criteria:

- If a study is rated as both 'Directly applicable' and 'Minor limitations' (by economic evaluation checklist) then it should be *included* in the guideline. An economic evidence table should be completed and it should be included in the economic profile
- If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be *excluded* from the guideline. It should not be included in the economic profile and there is no need to include an evidence table.
- If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is *discretion* over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline.

Also exclude:

- Unpublished reports
- Abstract-only studies
- Letter
- Editorials
- Reviews of economic evaluations[a]
- Foreign language articles

Where there is discretion

The health economist should be guided by the following hierarchies.

Setting:

- UK NHS
- OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden)
- OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland)
- Non-OECD settings (always 'Not applicable')

Economic study type:

- Cost-utility analysis
- Other type of full economic evaluation (cost-benefit analysis or cost-effectiveness analysis)
- Comparative cost analyses
- Cost of illness studies (always 'Not applicable')

Year of analysis:

- The more recent the study, the more applicable it is

Quality of effectiveness data used in the economic analysis:

- The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

a Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.