Appendix M: Cost-effectiveness analysis – Topical therapies for the treatment of mild to moderate plaque psoriasis of the trunk and limbs

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M.1 Introduction

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 indicated that some interventions, such as combined or concurrent vitamin D or 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 is important to consider whether these additional costs are justified by additional health benefits in terms of improved quality of life.

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[1] was based on only one trial and included only two of the interventions of interest (dithranol and calcipotriol). The analysis by Oh and colleagues[2] was quite old and had a fairly confusing model structure. The analysis by Bottomley and colleagues,[3] 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 limitations of the available economic evidence and the importance of this area in clinical practice, the GDG considered the development of an original cost-effectiveness model to evaluate topical therapies to be a high priority. The decision modelling presented here was developed in close collaboration between the health economist, NCGC technical team and GDG members.

M.2 Methods

M.2.1 Model overview

The analysis set out to evaluate the comparative cost-effectiveness of different topical therapy sequences used in the treatment of individuals with chronic plaque psoriasis. A cost-utility analysis was undertaken in line with the methods of the NICE reference case. QALYs were calculated using utility weights from EQ-5D responses and UK public valuations. Costs were considered from a UK National Health Service and Personal Social Services perspective and expressed in 2011 UK sterling. Healthcare costs associated with starting, maintaining and/or switching topical therapies as well as longer term costs of failing topical therapy were all included in the model.

The cost-effectiveness analysis must be relevant for decision-making over the longer term, as most people with psoriasis can be expected to require treatment for much of their lives. However, the evidence available for topical treatments is of short term duration and it would inappropriate to extrapolate for many years beyond treatment initiation given that the long term pathway of care is dependent on disease severity, access to specific facilities, patient preference and so on. Therefore, a 1-year time horizon was considered sufficiently long enough to capture the relevant costs and benefits associated with competing topical treatments.

To enable direct comparisons of treatments to be made based on the results of all relevant clinical trials, a network meta-analysis was performed and used to inform estimates of response (defined as clear or nearly clear) to treatment.

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.

All analyses were conducted probabilistically, thus capturing the imprecision and uncertainty around input parameter point estimates (i.e. mean/median odds ratios, utility weights, etc). A probability distribution was defined for various model inputs and when the model is run, a value for each input was randomly selected from its specific probability distribution simultaneously and costs and QALYs were calculated using these random values. The model is run repeatedly – in this case 5,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals. In addition, a series of one-way sensitivity analyses were run in order to test the effect of certain structural or variable uncertainties.

M.2.1.1 Comparators

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. Table 1 presents the list of possible first, second and third line treatments which may be combined in a sequence.

Table 1: 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
Two-compound formulation product (TCF) OD	TCF OD	TCF 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 would not come after a failure of once daily two-compound formulation product;
- 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 or once daily two-compound formulation product;

- 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 or combined product containing betamethasone dipropionate and calcipotriol monohydrate).

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.

M.2.1.2 Population

The analysis set out to evaluate the comparative cost-effectiveness of different topical therapy sequences used in the treatment of individuals with mild to moderate chronic plaque psoriasis.

M.2.1.3 Time horizon, perspective, discount rates used

The analysis took a UK National Health Service and Personal Social Services costing perspective, with costs expressed in 2011 UK sterling. A 1-year time horizon was considered clinically relevant and sufficiently long enough to capture important costs and consequences of first-line treatment in primary care. Since the time horizon was 1 year, no discounting rates were applied to either costs or benefits.

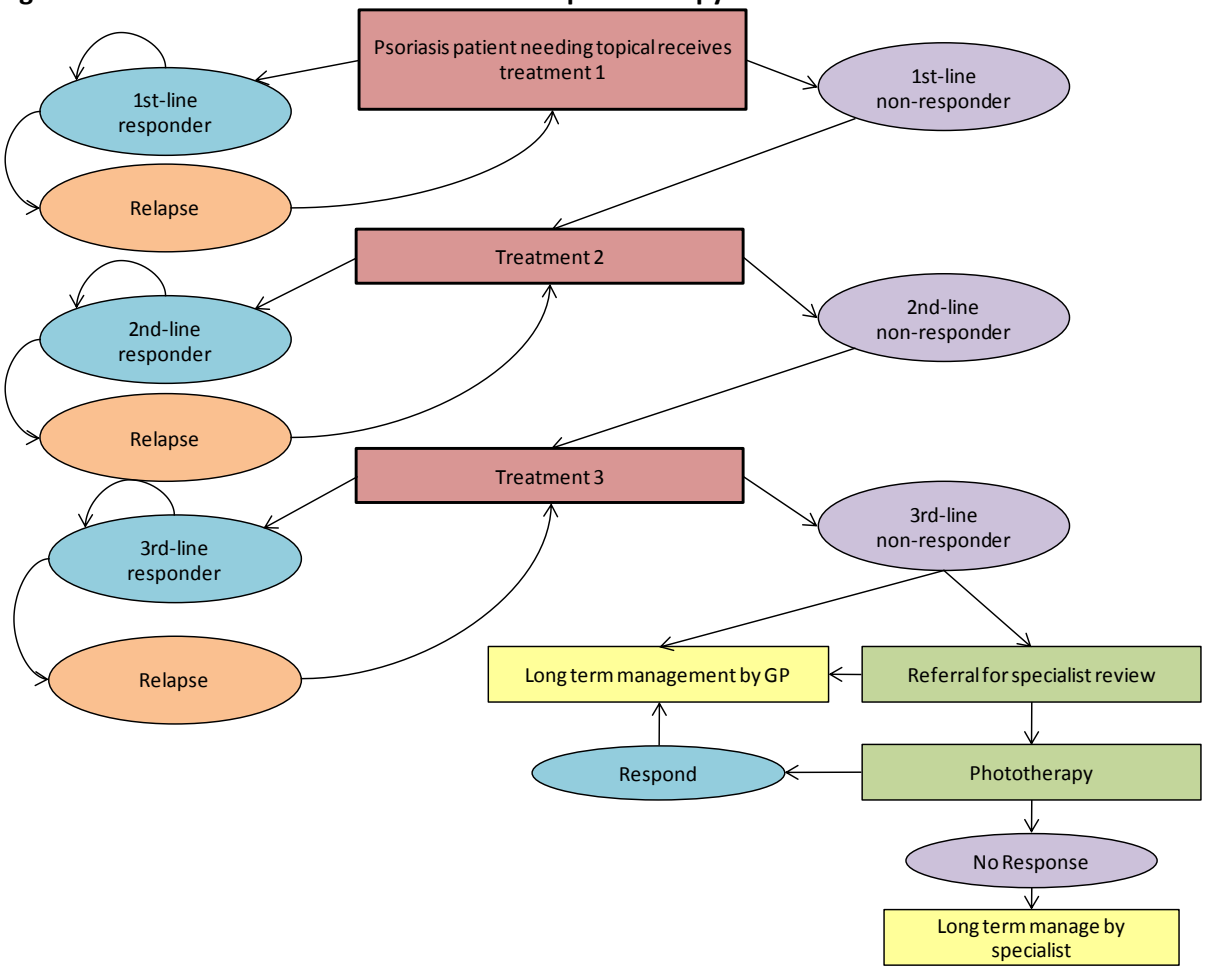
M.2.2 Approach to modelling

M.2.2.1 Model structure

A Markov model was constructed in TreeAge Pro 2009 to capture the different costs and effects associated with a given sequence of topical treatments. It was built to reflect transitions between a set of mutually exclusive health states, defined by response and non-response to treatment. The Markov model and how patients move through the pathway is illustrated in Figure 1. The structure of the model developed by the NCGC was adapted from the model developed by Bottomley and colleagues[3] and was validated by the GDG as a reasonable reflection of current clinical practice.

The consequences of a given topical treatment are reflected as a set of possible transitions between health states over a series of discrete time periods, called cycles. In Figure 1, health states are depicted as ovals and interventions are depicted as rectangles. 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 1: Markov model of treatment with topical therapy



Source: <Insert Source text here>

The model assumes that all hypothetical patients commence treatment with a given topical and experience one of two outcomes: response (defined as clearance/near clearance of their psoriasis) or no response (defined as something less than clearance/near clearance of their psoriasis). Patients who achieve clearance/near clearance are assumed to stop treatment and either maintain clearance/near clearance in the absence of treatment or they relapse. Patients who relapse are assumed to resume treatment with the same topical and again face a probability of responding or not responding. Patients who fail to achieve clearance on a given topical 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 will undergo a course of phototherapy and if they respond, they are discharged to their GP for long-term management.

M.2.2.2 Uncertainty

All analyses were conducted probabilistically, thus capturing the imprecision and uncertainty around input parameter point estimates (i.e. mean/median odds ratios, utility weights, etc). A probability distribution was defined for various model inputs and when the model is run, a value for each input was randomly selected from its specific probability distribution simultaneously and costs and QALYs

were calculated using these random values. The model is run repeatedly – in this case 5,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals. In addition, a series of one-way sensitivity analyses were run in order to test the effect of certain structural or variable uncertainties.

M.2.3 Model inputs

M.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Summary of base-case model inputs

Input	Data	Source
Comparators	See Table 1	
Population	Individuals with mild to moderate chronic plaque psoriasis	
Perspective	UK NHS and & PSS	NICE reference case[4]
Time horizon	1 year	
Discounting	Not applicable (a)	

(a) 3.5% annual discounting applied to costs and benefits in sensitivity analyses extending time horizon

Table 3: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Source/Notes
Baseline Risk (Placebo/vehicle BD)			
Clear/nearly clear	12.5%	Beta: α=116; β=811	Network meta-analysis (see Appendix K)
Efficacy (Odds ratio compared to Baseline)			
Vitamin D or vitamin D analogue OD	5.26	10,000 simulated odds ratios from the NMA were used	Network meta-analysis (see Appendix K)
Vitamin D or vitamin D analogue BD	8.21		Network meta-analysis (see Appendix K)
Potent corticosteroid OD	6.27		Network meta-analysis (see Appendix K)
Potent corticosteroid BD	11.49		Network meta-analysis (see Appendix K)
Combined vitamin D and potent corticosteroid OD	16.92		Network meta-analysis (see Appendix K)
Concurrent vitamin D or vitamin D analogue and potent corticosteroid	13.03		Network meta-analysis (see Appendix K)
Coal Tar BD	8.33		Network meta-analysis (see Appendix K)
Dithranol OD	5.16		Network meta-analysis (see Appendix K)
Relapse for all topicals			

Parameter description	Point estimate	Probability distribution	Source/Notes
All topical therapies	35.5%	Beta: α=192; β= 137	Based on mean from RCTs; test range in sensitivity analysis
Probability of specialist referral and subsequent management			
Referral for specialist review	60%		Dermatology Health Care Needs Assessment [5]
Topicals with specialist advice	70%		Assumption
Treated with phototherapy	30%		Assumption
Probability of response to phototherapy	86.7%	Beta: α=78; β=12	Clinical evidence review for phototherapy (Chapter 8)(Dawe 1998[6]; Hallaji 2010[7]; Cameron 2002[8])
Health-related Quality of Life (a)			
Response - Clear/nearly clear	0.89	Gamma: α= 25 β= 227.27	Bottomley 2007[3]
Non-response – Not clear/nearly clear	0.85	Gamma: α= 25 β= 625	Assumption
Baseline	0.80	Gamma: α= 25 β= 500	Bottomley 2007[3]
Resource use			
4 weeks of topical treatment			
Vehicle BD	152.8 g	Gamma: α=25.00 β=6.11	Guenther 2002[9]
Vitamin D or vitamin D analogue OD	142.0 g	Gamma: α=25.00 β=5.68	Kaufman 2002[10]
Vitamin D or vitamin D analogue BD	164.9 g	Gamma: α=25.00 β=6.60	Douglas 2002 [11]and Guenther 2002[9]
Potent corticosteroid OD	140.0 g	Gamma: α=25.00 β= 5.60	Kaufman 2002[10]
Potent corticosteroid BD	144.5 g	Gamma: α=25.00 β=5.78	Douglas 2002[11]
Combined vitamin D and potent corticosteroid (TCF product) OD	134.0 g	Gamma: α=25.00 β=5.36	Kaufman 2002[10]
Concurrent vitamin D or vitamin D analogue and potent corticosteroid	160.9 g (80.45 g each)	Gamma: α=25.00 β=6.44	Bottomley 2007[3]
Coal Tar	339.2 g	Gamma: α=25.00 β=13.57	Assumed same as Dithranol

Parameter description	Point estimate	Probability distribution	Source/Notes
Dithranol OD	339.2 g	Gamma: α=25.00 β=13.57	van de Kerkhof 2006[12]
Healthcare consultations			
GP consultation following non-response to topical treatment	1 per treatment change		Bottomley 2007[3] and assumption
Specialist outpatient consultation	1 following failure of 3 topicals		Assumption
Phototherapy sessions	24 per course		Median treatments to clear from phototherapy evidence review (Chapter 8)
Long term management by GP	1 visit per 3 months		Assumption
Cost (£)			
Unit cost of topical treatment			
Vehicle	500 g = £6.32		Diprobase
Vitamin D	100 g = £13.87		100 g Silkis; 120 g Dovonex = £23.10
Potent corticosteroid	100 g = £4.05; 30 g = £1.43		Betnovate cream or ointment
Combined vitamin D and potent corticosteroid (TCF product)	120 g = £61.27; 60 g = £32.99		Dovobet ointment; Dovobet gel: £67.79 (120 g), £36.50 (60 g)
Coal Tar	225 g = £9.42		Psoriderm cream
Dithranol 0.1%	50 g = £3.77		Dithrocream
Dithranol 0.25%	50 g = £4.04		Dithrocream
Dithranol 0.5%	50 g = £4.66		Dithrocream
Dithranol 1%	50 g = £5.42		Dithrocream
Dithranol 2%	50 g = £6.79		Dithrocream
Dithranol 3%	50 g = £16.79		Micanol
Unit cost of healthcare consultations			
GP consultation	£28		PSSRU 2010[13]
Specialist outpatient consultation	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[14]
Specialist outpatient nurse consultation (first visit)	£81	lognormal: log of mean = 4.40 se of logs = 0.03	NHS Reference costs 2009-10[14]
Specialist outpatient nurse consultation (follow-up visit)	£64	lognormal: log of mean = 4.15 se of logs =	NHS Reference costs 2009-10[14]

Parameter description	Point estimate	Probability distribution	Source/Notes
		0.05	
Phototherapy session (JC29Z)	£82	lognormal: log of mean = 4.40 se of logs = 0.08	NHS Reference costs 2009-10[14]

(a) See Section M.2.3.5 for more details on how utilities were parameterised in the model

M.2.3.2 Baseline event rates

Creams and emollients with no active ingredient are a typical first-line therapy for patients presenting with plaque psoriasis. Although the primary objective of this model is to identify cost-effective sequences of topical therapies with active ingredients, it is useful to compare all strategies to a baseline probability of achieving clearance with a topical without an active ingredient. The absolute probability of achieving clearance or near clearance with twice daily vehicle/placebo was calculated by aggregating the number of people achieving clear/nearly clear across the twice daily vehicle/placebo arms of randomised controlled trials included in the systematic review of topical therapies and dividing by the aggregate sample size from the same arms. This resulted in a probability of 12.5% (95% CI: 10.4% to 14.6%) for achieving clear/nearly clear. For the probabilistic analysis, uncertainty in the risk parameter for vehicle/placebo was incorporated using a beta distribution (α=116; β=811).

M.2.3.3 Relative treatment effects

In order to estimate the effectiveness for all other comparators in the model, the treatment effect estimates from the network meta-analysis (see Appendix K) were applied to the baseline probabilities outlined above. In the base case, the estimates relating to the investigator assessed outcome (IAGI/PGA) were used. The effect estimates derived from the patient assessed outcome (PAGI) were used in a sensitivity analysis. In a further sensitivity analysis, the data from the network meta-analysis using all available data was used. The odds ratios used in the base case and each sensitivity analysis are presented in Table 4.

Table 4: Treatment effects

	Odds ratio vs placebo (95% CrI)		
Intervention	**Base Case**	**SA – PAGI**	**SA – all data**
Vitamin D or vitamin D analogue OD	5.26 (1.74 to 16.9)	3.30 (0.99 to 11.2)	4.93 (1.9 to 13.2)
Vitamin D or vitamin D analogue BD	8.21 (4.44 to 15.3)	6.50 (2.72 to 16.0)	7.09 (4.1 to 12.1)
Potent corticosteroid OD	6.27 (1.58 to 23.4)	7.76 (1.65 to 39.1)	5.98 (1.84 to 19.0)
Potent corticosteroid BD	11.49 (5.379 to 25.0)	5.54 (1.99 to 16.6)	11.75 (5.97 to 23.8)
TCF OD	16.92 (5.53 to 50.3)	12.9 (4.25 to 41.2)	16.1 (6.68 to 39.2)
Concurrent am/pm	13.03 (3.96 to 44.8)	9.799 (2.18 to 44.6)	11.5 (3.75 to 35.5)
Coal Tar BD	8.33 (2.23 to 33)	2.96 (0.81 to 11.3) (a)	4.15 (1.41 to 12.4)
Dithranol OD	5.16 (1.88 to 14.4)	2.96 (0.81 to 11.3)	4.44 (1.76 to 11.3)

(a) In the absence of any patient reported outcomes for coal tar treatments, it was assumed that twice daily coal tar had a risk ratio equal to that of once daily dithranol.

To calculate the absolute probability of response to a given topical treatment, the odds ratio of that intervention compared to twice daily placebo from the network meta-analysis was converted into a

relative risk and applied to the 12.5% baseline risk (e.g. probability of response to twice daily placebo) using the following formula:

Where P_T is probability or response to a given treatment; P_0 is baseline probability of response and

Where: OR is the odds ratio of the treatment compared to P_0, the baseline probability. The estimated probabilities of response for the base case and each sensitivity analysis are presented in Table 5.

For the probabilistic implementation of the analysis, uncertainty in the comparative treatment effects is incorporated by using 10,000 of the simulated odds ratios from the network meta-analysis. Using the simulated outputs allows us to preserve the joint posterior distribution from the network meta-analysis and any correlation of treatment effects.

Table 5: Probability of response

	Probabilities of response		
Intervention	**Base Case**	**SA - PAGI**	**SA - all data**
Vehicle BD	12.5%	14.4%	12.5%
Vitamin D or vitamin D analogue OD	42.9%	35.7%	41.3%
Vitamin D or vitamin D analogue BD	54.0%	52.2%	50.3%
Potent corticosteroid OD	47.2%	56.6%	46.1%
Potent corticosteroid BD	62.1%	48.2%	62.7%
TCF OD	70.7%	68.5%	69.7%
Concurrent am/pm	65.1%	62.2%	62.2%
Coal Tar BD	54.3%	33.2%	37.2%
Dithranol OD	42.4%	33.2%	38.8%

Independent treatment effects were assumed across all interventions regardless of when they came in a sequence. In other words, the effectiveness of any topical as a second line intervention was not affected by what treatment may have come before.

Early versus late response

The data used to estimate the overall probabilities of response to treatment (Table 5) were based on trials of varying duration, 3 to 12 weeks follow-up. In the clinical review, we looked for evidence that would suggest when the appropriate time to assess response to treatment was. Where trials were of longer duration (i.e. 8 to 12 weeks) the evidence suggested that patients were still improving between 4 and 8 weeks. On that basis the GDG felt it would be inappropriate to assume that a) everyone who will respond will do so within 4 weeks and that b) patients who were not clear/nearly clear at the end of week 4 should discontinue treatment and be classified as a non-responders. Therefore, the model assumes that patients will be treated with a given topical for up to 8 weeks. If they respond in the first 4 weeks, then they are assumed to discontinue treatment. If they have not yet responded, then they are assumed to carry on for a further 4 weeks after which they discontinue having responded or not responded.

On that basis, where data from trials with longer follow-up was available, we looked to estimate what proportion of patients who responded by the end of follow-up had done so within the first 4 weeks or the last 4 weeks. The data with which to estimate this was patchy, but one trial[15] included

our main 4 comparators (vehicle, potent corticosteroid, vitamin D or vitamin D analogue and two-compound formulation product) and reported response rates at both 4 weeks and 8 weeks. The data showed that a small proportion of people had responded to vehicle in the first 4 weeks, but by week 8 the number of responders was zero. On that basis, it was assumed that any response to placebo will occur in the first 4 weeks, with no additional responders in the following 8 weeks. For topicals with active ingredients, the data from Fleming 2010 indicated that of all responders to once daily vitamin D or vitamin D analogue at 8 weeks, one-third had achieved clearance by week 4. This figure was 57% and 59% for once daily potent corticosteroids and two-compound formulation product, respectively.

The proportions of early (0 to 4 weeks) and late (5 to 8 weeks) responders from Fleming 2010 were applied to the overall response figures generated from the network meta-analysis in order to estimate the probabilities of response in the first 4 weeks of treatment and the second 4 weeks of treatment (presented in Table 6). In the absence of data, the assumption was made that the proportions of early and late responders is the same for once and twice daily application of a given topical. In other words, this assumes that twice daily application of a topical does not induce response earlier than once daily application of the same topical. This assumption was validated by GDG member experience, which was that frequency of application did not have a demonstrable effect on speed of response.

Table 6: Probabilities of response: overall, early and late

Intervention	Overall probability of achieving response	Of all responders, proportion who will respond in first 4 weeks	Probability of early response (0 to 4 wks)	Probability of late response (5 to 8 wks)
Placebo BD	12.5%	100%	12.5%	0%
Vitamin D or vitamin D analogue OD	42.9%	33%	14.3%	33.4%
Vitamin D or vitamin D analogue BD	54.0%	33%	18.0%	43.9%
Potent corticosteroid OD	47.2%	57%	26.8%	27.9%
Potent corticosteroid BD	62.1%	57%	35.3%	41.5%
TCF OD	70.7%	59%	41.6%	49.9%
Concurrent Vit D and steroid	65.1%	57%	36.9%	44.6%
Coal Tar BD	54.3%	50%	27.2%	37.3%
Dithranol OD	42.4%	50%	21.2%	26.9%

There was no trial data to inform the early compared to late responses for concurrent vitamin D or vitamin D analogue and potent corticosteroid treatment, coal tar or dithranol. In the absence of data, the GDG made the assumption that the proportion of early and late responders to concurrent vitamin D or vitamin D analogue and potent corticosteroid was likely to be the same as for potent steroid given that this is the component most likely to drive rate of response. For dithranol, graphs from Hutchinson 2000[16] were judged to suggest that by the end of week 4, half of overall 8-week improvement in terms of IAGI and PASI had been achieved. Based on this, the assumption was made that the split between early and late response for dithranol was 50/50. Finally, in the absence of data, the GDG made the assumption that the early versus late breakdown for coal tar was the same as for dithranol.

M.2.3.4 Relapse

Psoriasis is a relapsing and remitting chronic condition and achievement of clearance/near clearance with active treatment has no long-term effect on the natural history of chronic plaque psoriasis. The

RCT data with regard to relapse was quite sparse and inconsistent, due to a variety of factors including variable trial follow-up and differences in the definition of relapse. For the economic model, the GDG defined relapse as any deterioration to the point at which retreatment is required.

Given the lack of data, the GDG considered that there was little evidence to suggest any major differences between the proportions of patients relapsing or the time spent clear before relapsing following clearance with different topical treatments. The probability of relapse was set at 35.5% for all interventions and was varied in a sensitivity analysis. Average risk of relapse at 8 weeks follow-up across the trials where the outcome was reported was 58.4%. Uncertainty in this estimate for the probabilistic analysis was captured using a beta distribution (α=192; β=137). Assuming that the rate of relapse was constant over the 8 weeks, this translates to a 4-week risk of 35.5%.

It has been assumed that patients are at risk of relapse at any point following remission. In other words, patients who respond to treatment in the first 4 weeks of treatment may relapse within 4 weeks of discontinuing treatment or during any 4 week cycle thereafter.

Referral and specialist management

Sixty percent of hypothetical patients failing to respond to their third topical therapy are assumed to be referred for specialist review. This is based on figures quoted in the Dermatology Health Care Needs Assessment[5], which states that 'although most patients have mild psoriasis, according to Nevitt and Hutchinson[17], 60% had been referred for specialist care at some point.' The 40 percent not referred onward are assumed to be managed by their GP for the time remaining in the model.

Among the 60 percent who are referred onward for consultation with a specialist, only 30% will be offered phototherapy. The other 70 percent will be given specialist advice and support about how to better manage their psoriasis with topical therapies. The 70/30 split used here is based on GDG opinion. In the GDG's experience, the majority of patients who are referred to secondary care do not actually need more aggressive treatments like phototherapy or systemic therapy. They indicated that for around 70 percent of patients referred, topical therapy is likely to offer the best balance of efficacy and safety and that the goal of care at this point is to ensure patients know how and when to use topicals to maximise their efficacy. The model assumes that they receive this advice and support at one outpatient consultation and are then discharged back to their GP for long term management.

The 30 percent who receive phototherapy have a probability of responding based up on the results of the clinical evidence review presented in section 6.12 of the full guideline. The clinical evidence shows that around 86.7% of patients who receive a course of narrowband UVB (2 or 3 times weekly) will achieve clearance. For the probabilistic analysis, uncertainty in this estimate of effect was captured using a beta distribution (α=78; β=12).

M.2.3.5 Utilities

Achievement of clearance or near clearance and associated utility gain was used in the model to determine the impact of psoriasis treatment on overall health. Estimates of utility gain were taken from a recent cost-utility analysis included in the health economic review[3]. The mean utility at baseline was 0.8 and mean utility gain associated with clearance/near clearance was 0.09. It is expected that patients who do not achieve clearance or near clearance will still experience some level of improvement on treatment; therefore, these patients also experience a modest utility gain. Bottomley and colleagues modelled a utility gain of 0.07 for non-responders, but the GDG considered this to be optimistic. They felt that the difference between responders and non-responders was likely to be greater, and therefore recommended a utility gain for non-responders compared to baseline to be slightly less, at 0.05. Due to the uncertainty in this parameter, it was varied in sensitivity analysis.

Table 7: Health state utility values and gains associated with response or non-response

Parameter description	Health state utility	Utility gain compared to baseline	Probability distribution (a)	Source/Notes
Response: Clear/nearly clear	0.89	0.07	Gamma: α= 25 β= 227.27 (b)	Bottomley 2007[3]
Non-response: Not clear/nearly clear	0.85	0.05	Gamma: α= 25 β= 625 (c)	Assumption Estimate from Bottomley 2007 used in a sensitivity analysis (0.07)
Baseline	0.80		Gamma: α= 25 β= 500 (d)	Bottomley 2007[3]

(a) Utility gains were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically (i.e. such that response was always greater than non-response, which was always greater than baseline). No error estimates were available from the literature, so it was assumed that the standard error for the distribution was 20% of the mean difference between health states.
(b) Distribution mean = 0.11, which was subtracted from perfect health (1.0-0.11=0.89)
(c) Distribution mean = 0.04, which was subtracted from response (0.89-0.04=0.85)
(d) Distribution mean = 0.05, which was subtracted from non-response (0.85-0.05=0.80)

Key assumptions about utilities in the model:

- Patients who do not achieve clearance at 4 weeks and continue on for a further 4 weeks of topical therapy will improve somewhat and therefore accrue the gain associated with non-responders.
- Patients who relapse following clearance lose the incremental gain between response and non-response (0.04) before resuming treatment.
- Patients who fail to respond and ultimately reach the point of requiring referral to a specialist or phototherapy return to their baseline level of utility (0.8).
- Patients managed long-term by either a GP or a specialist accrue the gain associated with non-responders.

M.2.3.6 Resource use and cost

Topical therapy

Resource use of alternative topical treatments was based on reported mean quantities of study drugs used by patients in the RCTs[9-12] at the end of 4-week treatment periods. No estimates were available to inform the mean usage of coal tar used twice daily. In the absence of data, we assumed that the mean usage for coal tar would be approximately equal to that of dithranol. No estimate from an RCT was available to inform the mean quantities of vitamin D analogue and potent corticosteroid when they are used concurrently (e.g. one in the morning and the other in the evening). In the cost-utility analysis by Bottomley and colleagues[3], they estimated mean usage for this strategy to be 160.9 g (95% CI: 140.7-181.1) based on an unpublished trial they held on file. We have taken this estimate for use in our model, assuming that the total usage is split evenly between vitamin D analogue and potent corticosteroid. Mean quantities and distribution parameters for the probabilistic analysis are presented in Table 8.

Unit costs of topicals (Table 9) were taken from the most recent BNF[18]. Given that the interventions were modelled assuming a class effect, the cost of topical had to be selected from a variety of

compounds, formulations and package sizes. For simplicity, we used the cost for the topical with the lowest unit cost per gram/millilitre.

Table 8: Mean quantities of topicals used per 4-week cycle

Topical therapy	Mean quantity used	Probability distribution	Source/Notes
Vehicle BD	152.8 g	Gamma: α=25.00 β=6.11	Guenther 2002[9]
Vitamin D or vitamin D analogue OD	142.0 g	Gamma: α=25.00 β=5.68	Kaufman 2002[10]
Vitamin D or vitamin D analogue BD	164.9 g	Gamma: α=25.00 β=6.60	Douglas 2002 [11]and Guenther 2002[9]
Potent corticosteroid OD	140.0 g	Gamma: α=25.00 β= 5.60	Kaufman 2002[10]
Potent corticosteroid BD	144.5 g	Gamma: α=25.00 β=5.78	Douglas 2002[11]
Combined vitamin D and potent corticosteroid (TCF product) OD	134.0 g	Gamma: α=25.00 β=5.36	Kaufman 2002[10]
Concurrent vitamin D or vitamin D analogue and potent corticosteroid	160.9 g (80.45 g each)	Gamma: α=25.00 β=6.44	Bottomley 2007[3]
Coal Tar	339.2 g	Gamma: α=25.00 β=13.57	Assumed same as Dithranol
Dithranol OD	339.2 g	Gamma: α=25.00 β=13.57	van de Kerkhof 2006[12]

Table 9: Unit costs of topical therapies

Topical therapy	Unit cost (£)	Source/Notes
Vehicle	500 g = £6.32	Diprobase
Vitamin D	100 g = £13.87	100 g Silkis; 120 g Dovonex = £23.10
Potent corticosteroid	100 g = £4.05; 30 g = £1.43	Betnovate cream or ointment
Combined vitamin D and potent corticosteroid (TCF product)	120 g = £61.27; 60 g = £32.99	Dovobet ointment; Dovobet gel: £67.79 (120 g), £36.50 (60 g)
Coal Tar	225 g = £9.42	Psoriderm cream
Dithranol 0.1%	50 g = £3.77	Dithrocream
Dithranol 0.25%	50 g = £4.04	Dithrocream
Dithranol 0.5%	50 g = £4.66	Dithrocream
Dithranol 1%	50 g = £5.42	Dithrocream

To calculate the per cycle cost of each topical, the mean quantities were converted into the cheapest combination of the number of packs of topical needed. For example, the mean 4-week dosage for twice daily potent corticosteroids was 144.5 g. The cheapest combination of packs needed to provide this quantity was one 100 g pack and two 30 g packs. The 4-week costs of topical treatment based on the mean quantities used are presented in Table 10.

During probabilistic implementation, dosages were drawn from topical specific gamma distributions fitted using the mean reported in the RCTs and a standard error assumed to be 20% of the mean. The model was built to ensure that the cheapest combination of packs, as outlined in the example above, could be calculated automatically for any sampled value. For example, if the sample value for twice daily potent corticosteroid was 180 g, then the cheapest combination would be automatically be calculated as two 100 g packs. Similarly, if the sampled value was 45 g, then the cheapest combination would be two 30 g packs.

Dithranol was assumed to be titrated up over the course of the first 4-week cycle, starting with 0.1% strength for the first week, followed by 0.25%, then 0.5% and finally 1%. The total dosage over the 4-week period was assumed to be distributed equally between the different strengths.

A different costing method was used for twice daily vehicle. Because the vehicle cream comes in large packs (500 g), the cost was applied per gram used during a 4-week cycle instead of per pack used during a 4-week cycle.

Table 10: Mean cost of 4-week topical treatment

Topical strategy	4-week cost
Vehicle	£1.93
Vitamin D or vitamin D analogue OD	£27.74
Vitamin D or vitamin D analogue BD	£27.74
Potent corticosteroid OD	£6.91
Potent corticosteroid BD	£6.91
Concurrent vitamin D or vitamin D analogue and potent corticosteroid	£17.92
TCF OD	£94.26
Coal tar BD	£18.84
Dithranol OD	Initial 4 weeks =£35.78 (upward titration) Subsequent 4 weeks =£37.94 (stable dose)

Health care consultations

It was assumed that following a failure (non-response) of a given topical treatment, patients returned to their GP for review and receive a second or third topical or referral for specialist review. Thus, each change in topical treatment will accrue a cost of a GP visit. Patients experiencing a relapse following successful treatment with a given topical are assumed to get a repeat prescription for the same topical without accruing the cost of a GP visit.

Sixty percent of patients who fail to respond to a third topical treatment are referred by their GP for specialist review. During the time spent between being referred and the specialist review, patients are assumed to maintain topical treatment, for which the average 4-week cost across all topical treatments was used (£29.78).

Each patient who is referred is seen by a consultant dermatologist in an outpatient clinic, thus accruing this cost. Based on GDG experience, it was assumed that 70% 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 other 30% are assumed to undergo a

course of phototherapy, thus accruing the cost of 24 sessions of narrowband UVB. Responders to narrowband UVB are assumed to be discharged to their GP for long-term management; non-responders are assumed to be managed in long-term specialist care.

In reality, some of this 30% referred for phototherapy might attend a day centre where they would undergo treatment with specialist applied topicals such as dithranol and crude coal tar. For reasons of pragmatism and simplicity, this alternative on the clinical care pathway was excluded from the base case. However, in a sensitivity analysis, we added in the likely costs of such treatments in order to observe how the results might change.

Table 11: Unit cost of health care consultations

Type of health care consultation	Health care resource use	Unit cost per consultation	Probability distribution	Source/Notes
GP consultation	• 1 per treatment change • 1 visit per 3 months for long term management	£28		PSSRU 2010[13]
Specialist outpatient consultation	• 1 following failure of 3 topicals	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[14]
Specialist outpatient nurse consultation (first visit)	• 1 following failure of 3 topicals	£81	lognormal: log of mean = 4.40 se of logs = 0.03	NHS Reference costs 2009-10[14]
Phototherapy session (JC29Z)	• 24 sessions per course	£82	lognormal: log of mean = 4.40 se of logs = 0.08	NHS Reference costs 2009-10[14]

M.2.4 Computations

The model was constructed in TreeAge Pro 2009 and was evaluated by cohort simulation. All hypothetical patients start treatment with a topical therapy and either achieve clearance or near clearance or do not. Following the achievement of clearance/near clearance, patients can subsequently relapse and upon resumption of the same topical therapy either respond or do not respond and move on to the next topical therapy in the sequence. Movement between health states in subsequent cycles is determined by the various probabilities described in the preceding sections. Each 4-week cycle the cohort spends in a given health state is counted.

Total QALYs were calculated from the above information as follows. Each 4-week cycle, the time spent in each health state of the model was weighted by the utility for that state. The QALYs per cycle were then discounted to reflect time preference. QALYs during year one were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle.

$$Total \quad discounted \quad QALYs = \sum_{t=1}^{i} \frac{Q(t)}{(1+r)^{t-1}}$$

Where: t=cycle number; i=maximum cycle number; Q(t) = QALYs in cycle t; r = discount rate

Total costs were calculated from the above information as follows. Each cycle, the time spent in each state of the model was multiplied by the costs for that state. The costs per cycle were then discounted to reflect time preference. Costs during year one were not discounted. The total discounted costs were the sum of the discounted costs per cycle.

$$Total\ \ discounted\ \ costs = \sum_{t=1}^{i} \frac{C(t)}{(1+r)^{t-1}}$$

Where: t=cycle number; i=maximum cycle number; C(t) = costs in cycle t; r = discount rate

The used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold, the result is considered to be cost effective. If both costs are lower and QALYs are higher, the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

When there are more than two comparators, as in this analysis, options were ranked in order of increasing cost and then options ruled out by dominance (i.e. those that were more costly and less effective than alternate strategies) or extended dominance (i.e. where a linear combination of other strategies could produce greater benefit at lower cost) were excluded before calculating ICERs. ICERs were calculated based on mean costs and effects as estimated during the probabilistic implementation of the model.

The effect of uncertainty in the results is reflected by the reporting of 95% confidence intervals around mean total costs and effects. Secondly, uncertainty was illustrated by estimating the probability a given AED was the optimal treatment option. For strategy X, this was calculated as

$$Net\ \ Benefit(X) = (QALYs(X) \times D) - Costs(X)$$

Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D=threshold

The decision rule then applied is that the strategy with the greatest net benefit is the cost-effective option at that threshold. That strategy is expected to provide the highest number of QALYs at an acceptable cost. The probability a given AED is optimal is calculated as the proportion of simulations where that option had the greatest net benefit at the specified threshold.

M.2.5 Sensitivity analyses

A series of one-way sensitivity analyses and scenario analyses were performed to assess how changes in one or more parameters or assumptions might change the conclusions of the analysis. In one set of sensitivity analyses, alternative estimates of treatment effects from the network meta-analyses (Appendix K) were used. In a second sensitivity analysis, the utility value associated with non-response was varied upward to match the estimate used by Bottomley and colleagues[3]. In a third set of sensitivity analyses, the quantity of combined product containing betamethasone dipropionate and calcipotriol monohydrate used over a 4 week treatment period was reduced to match the estimate used by Bottomley and colleagues. In a fourth series of sensitivity analyses, estimates of future resource use and cost were altered and the time horizon was lengthened. Finally, alternative assumptions about the comparators were used to explore what might be appropriate if there were concerns about safety or contraindications.

M.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of the model calculations.

M.3 Results

M.3.1 Base case

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 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 in Table 12.

Results showed that starting with concurrent potent corticosteroid and vitamin D or vitamin D analogue 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 betamethasone dipropionate and calcipotriol monohydrate 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 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 betamethasone dipropionate and calcipotriol monohydrate, although most effective, is very unlikely to be cost-effective.

Table 12: 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)

Mean costs and QALYs and their respective 95% confidence intervals for all strategies, ranked in order of mean net benefits at a £20,000 per QALY threshold, are presented in Table 13. These show 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 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.

A breakdown of total costs by type of resource use (i.e. topicals, GP visits, outpatient consultations, phototherapy) is presented for all modeled strategies in Table 14. Based on this disaggregation, it becomes clear that strategies with combined product containing betamethasone dipropionate and calcipotriol monohydrate or vitamin D or vitamin D analogue have relatively high topical costs, some of which are offset by reduced downstream costs in terms of consultations with specialists and courses of phototherapy. Strategies with potent corticosteroids offered alone or in combination with vitamin D or vitamin D analogue (concurrent therapy) show similar downstream costs as strategies involving combined product containing betamethasone dipropionate and calcipotriol monohydrate, but because their acquisition cost is dramatically lower, the overall total cost is much lower.

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 corticosteroid and vitamin D 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 is most likely to be cost-effective, whereas starting with once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate is very unlikely to be cost-effective.

Table 13: Mean total costs and QALYs for all modelled comparators

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @£20k
PS BD - Concurrent - Coal Tar BD	226	109 to 404	0.8487	0.8022 to 0.8877	16748
Concurrent - PS BD - Coal tar BD	236	125 to 407	0.8491	0.8024 to 0.8886	16747
PS BD - Concurrent - Vit D BD	238	117 to 412	0.8486	0.8019 to 0.8875	16735
Concurrent - PS BD - Vit D BD	247	133 to 415	0.8490	0.8022 to 0.8885	16734
Concurrent - PS BD - Vit D OD	262	134 to 445	0.8487	0.8019 to 0.8884	16712
PS BD - Vit D BD - Concurrent	255	137 to 420	0.8483	0.8015 to 0.8874	16712
Concurrent - Vit D BD - PS BD	272	150 to 435	0.8488	0.8021 to 0.8884	16705
PS BD - Concurrent - Dithranol OD	267	127 to 466	0.8483	0.8016 to 0.8875	16699
Concurrent - PS BD - Dithranol OD	276	140 to 467	0.8487	0.8021 to 0.8884	16698
PS BD - Vit D OD - Concurrent	268	139 to 450	0.8479	0.8014 to 0.8871	16690
PS OD - PS BD - Coal Tar BD	249	110 to 431	0.8466	0.8004 to 0.8861	16682
PS BD - Vit D BD - Coal Tar BD	279	147 to 449	0.8478	0.8009 to 0.8871	16678
Vit D BD - PS BD - Concurrent	276	178 to 422	0.8476	0.8008 to 0.8870	16676
Concurrent - Vit D BD - Coal Tar BD	301	158 to 498	0.8485	0.8017 to 0.8881	16669
PS OD - Concurrent - Coal tar BD	269	115 to 484	0.8468	0.8004 to 0.8862	16667
Vit D BD - Concurrent - PS BD	289	190 to 436	0.8477	0.8010 to 0.8870	16665

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @£20k
PS OD - PS BD - Vit D BD	264	122 to 441	0.8464	0.8002 to 0.8859	16665
Concurrent - Vit D BD - PS OD	302	155 to 497	0.8482	0.8015 to 0.8880	16663
PS BD - Vit D BD - TCF OD	319	172 to 510	0.8487	0.8019 to 0.8877	16654
PS BD - Vit D OD - Coal Tar BD	295	151 to 471	0.8474	0.8007 to 0.8865	16652
PS OD - Concurrent - Vit D BD	284	123 to 493	0.8467	0.8002 to 0.8860	16650
Concurrent - Vit D BD - TCF OD	339	175 to 561	0.8493	0.8028 to 0.8888	16646
Vit D OD - PS BD - Concurrent	285	173 to 452	0.8465	0.8004 to 0.8859	16645
Vit D BD - PS BD - Coal Tar BD	300	187 to 453	0.8471	0.8003 to 0.8862	16642
PS BD - Vit D OD - Vit D BD	310	165 to 487	0.8472	0.8003 to 0.8865	16635
PS OD - PS BD - Vit D OD	285	117 to 483	0.8460	0.7994 to 0.8856	16634
Vit D OD - Concurrent - PS BD	299	185 to 464	0.8466	0.8004 to 0.8859	16633
Vit D BD - PS OD - PS BD	302	187 to 454	0.8467	0.8000 to 0.8861	16631
PS OD - Vit D BD - PS BD	294	149 to 461	0.8462	0.7998 to 0.8856	16630
PS BD - TCF OD - Coal Tar BD	353	197 to 545	0.8492	0.8027 to 0.8881	16630
Vit D BD - Concurrent - Coal tar BD	318	199 to 497	0.8474	0.8008 to 0.8866	16629
Vit D BD - PS OD - Concurrent	311	182 to 491	0.8468	0.8000 to 0.8860	16625
PS OD - Vit D BD - Concurrent	303	145 to 498	0.8464	0.7999 to 0.8856	16625
Concurrent - TCF OD - Coal tar BD	371	194 to 601	0.8497	0.8032 to 0.8891	16624
PS BD - Vit D OD - TCF OD	342	175 to 555	0.8482	0.8017 to 0.8873	16622
Vit D BD - PS BD - TCF OD	339	214 to 513	0.8479	0.8014 to 0.8871	16620
PS BD - Vit D BD - Dithranol OD	328	172 to 520	0.8473	0.8002 to 0.8869	16618
PS OD - PS BD - Dithranol OD	302	138 to 498	0.8460	0.7994 to 0.8855	16618
PS BD - TCF OD - Vit D BD	364	204 to 554	0.8491	0.8023 to 0.8880	16618
Concurrent - Vit D BD - Dithranol OD	347	175 to 558	0.8480	0.8014 to 0.8877	16614
Concurrent - TCF OD - Vit D BD	381	197 to 610	0.8497	0.8030 to 0.8892	16612
PS BD - Concurrent - Referral	335	161 to 548	0.8472	0.8004 to 0.8864	16609
Concurrent - PS BD - Referral	344	176 to 551	0.8476	0.8006 to 0.8874	16608
Vit D OD - PS BD - Coal tar OD	311	184 to 474	0.8460	0.7999 to 0.8854	16608
Vit D BD - Concurrent - TCF OD	356	216 to 560	0.8481	0.8014 to 0.8874	16606
PS OD - Concurrent - Dithranol OD	320	134 to 556	0.8463	0.7996 to 0.8856	16606
PS OD - Vit D OD - PS BD	311	139 to 500	0.8456	0.7992 to 0.8854	16602
PS OD - Vit D OD - Concurrent	323	134 to 557	0.8458	0.7992 to 0.8851	16593
Vit D OD - Concurrent - Coal tar BD	332	193 to 537	0.8462	0.8000 to 0.8857	16592
Vit D OD - PS BD - Vit D BD	327	202 to 487	0.8458	0.7995 to 0.8854	16589
Vit D OD - PS OD - PS BD	318	177 to 493	0.8454	0.7991 to 0.8849	16589

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @£20k
PS BD - TCF OD - Dithranol OD	389	214 to 599	0.8488	0.8019 to 0.8880	16587
PS BD - Vit D OD - Dithranol OD	350	181 to 545	0.8468	0.7998 to 0.8863	16586
Vit D BD - PS OD - Coal Tar BD	340	198 to 525	0.8462	0.7999 to 0.8856	16584
Vit D BD - PS BD - Dithranol OD	348	217 to 521	0.8466	0.7996 to 0.8861	16584
PS OD - Vit D BD - Coal Tar BD	332	156 to 531	0.8458	0.7993 to 0.8853	16584
Concurrent - TCF OD - Dithranol OD	405	205 to 658	0.8494	0.8028 to 0.8890	16582
Vit D OD - PS OD - Concurrent	330	172 to 549	0.8455	0.7991 to 0.8849	16581
Vit D OD - PS BD - TCF OD	359	209 to 556	0.8468	0.8005 to 0.8863	16577
TCF OD - PS BD - Coal Tar BD	428	290 to 575	0.8502	0.8041 to 0.8894	16576
Vit D OD - Concurrent - Vit D BD	347	201 to 540	0.8461	0.7996 to 0.8855	16575
Vit D BD - Concurrent - Dithranol OD	364	217 to 557	0.8469	0.8004 to 0.8864	16574
TCF OD - PS BD - Vit D BD	438	300 to 581	0.8501	0.8038 to 0.8892	16564
Vit D OD - Concurrent - TCF OD	379	207 to 625	0.8470	0.8009 to 0.8863	16561
Vit D OD - Vit D BD - PS BD	357	236 to 505	0.8456	0.7994 to 0.8852	16555
Vit D BD - PS OD - TCF OD	391	217 to 611	0.8471	0.8006 to 0.8863	16552
PS OD - Vit D BD - TCF OD	383	177 to 620	0.8467	0.8000 to 0.8859	16551
Vit D OD - Vit D BD - Concurrent	367	230 to 545	0.8458	0.7993 to 0.8853	16548
PS OD - Vit D OD - Coal tar BD	355	148 to 582	0.8451	0.7989 to 0.8849	16548
TCF OD - PS BD - Vit D OD	453	303 to 607	0.8498	0.8035 to 0.8891	16542
Vit D OD - PS BD - Dithranol OD	366	217 to 547	0.8454	0.7989 to 0.8851	16541
TCF OD - Vit D BD - PS BD	461	322 to 602	0.8499	0.8035 to 0.8892	16538
Vit D OD - PS OD - Coal tar BD	362	185 to 575	0.8449	0.7987 to 0.8845	16535
TCF OD - PS BD - Dithranol OD	463	310 to 624	0.8498	0.8034 to 0.8889	16533
Vit D BD - TCF OD - PS BD	432	296 to 590	0.8482	0.8016 to 0.8872	16531
Vit D OD - Concurrent - Dithranol OD	385	213 to 604	0.8457	0.7991 to 0.8852	16528
PS OD - Vit D OD - Vit D BD	375	162 to 588	0.8450	0.7984 to 0.8847	16525
PS OD - TCF OD - Coal Tar BD	421	200 to 660	0.8473	0.8007 to 0.8868	16524
Concurrent - Vit D BD - Referral	421	218 to 643	0.8468	0.7998 to 0.8866	16515
PS BD - Vit D BD - referral	407	233 to 592	0.8460	0.7989 to 0.8855	16513
Vit D OD - PS OD - Vit D BD	381	200 to 580	0.8447	0.7985 to 0.8842	16513
Vit D BD - PS OD - Dithranol OD	400	233 to 590	0.8456	0.7989 to 0.8852	16512
PS OD - Vit D BD - Dithranol OD	392	191 to 598	0.8452	0.7983 to 0.8847	16511
PS OD - TCF OD - Vit D BD	434	207 to 670	0.8472	0.8004 to 0.8864	16509

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @£20k
TCF OD - Vit D BD - Coal Tar BD	486	331 to 650	0.8496	0.8035 to 0.8888	16507
PS BD - TCF OD - Referral	450	254 to 672	0.8478	0.8012 to 0.8870	16507
Concurrent - TCF OD - Referral	463	232 to 743	0.8485	0.8013 to 0.8880	16506
Vit D OD - Vit D BD - Coal Tar BD	397	248 to 574	0.8451	0.7990 to 0.8846	16506
PS OD - Vit D OD - TCF OD	417	161 to 719	0.8461	0.7994 to 0.8857	16505
PS OD - PS BD - Referral	387	190 to 583	0.8446	0.7979 to 0.8844	16505
PS OD - Concurrent - Referral	399	169 to 649	0.8450	0.7980 to 0.8845	16500
Vit D BD - TCF OD - Coal Tar BD	458	307 to 641	0.8479	0.8013 to 0.8869	16499
TCF OD - Vit D BD - PS OD	490	325 to 659	0.8493	0.8025 to 0.8885	16497
Vit D OD - Vit D BD - PS OD	401	235 to 589	0.8447	0.7983 to 0.8842	16494
Vit D OD - PS OD - TCF OD	424	201 to 711	0.8459	0.7996 to 0.8851	16493
Vit D OD - TCF OD - PS BD	458	291 to 638	0.8470	0.8009 to 0.8865	16483
Vit D BD - PS BD - Referral	428	279 to 592	0.8453	0.7983 to 0.8847	16478
Vit D BD - Concurrent - Referral	438	262 to 643	0.8457	0.7989 to 0.8854	16476
Vit D OD - Vit D BD - TCF OD	450	273 to 660	0.8461	0.7999 to 0.8855	16472
PS OD - TCF OD - Dithranol OD	466	214 to 730	0.8468	0.7999 to 0.8860	16470
PS BD - Vit D OD - REferral	437	248 to 628	0.8453	0.7986 to 0.8850	16469
PS OD - Vit D OD - Dithranol OD	424	175 to 672	0.8444	0.7979 to 0.8842	16464
TCF OD - Vit D BD - Dithranol OD	526	354 to 701	0.8492	0.8026 to 0.8884	16458
TCF OD - PS BD - Referral	525	352 to 698	0.8489	0.8024 to 0.8882	16452
Vit D OD - PS OD - Dithranol OD	431	217 to 664	0.8441	0.7976 to 0.8838	16452
Vit D BD - TCF OD - Dithranol OD	498	330 to 694	0.8474	0.8008 to 0.8869	16451
Vit D OD - TCF OD - Coal Tar BD	488	300 to 704	0.8467	0.8008 to 0.8862	16446
Vit D OD - Vit D BD - Dithranol OD	459	288 to 644	0.8445	0.7981 to 0.8842	16431
Vit D OD - TCF OD - Vit D BD	502	308 to 709	0.8466	0.8004 to 0.8859	16430
Vit D OD - PS BD - Referral	454	283 to 629	0.8439	0.7975 to 0.8839	16424
Vit D OD - Concurrent - Referral	467	253 to 697	0.8443	0.7975 to 0.8839	16418
Vit D OD - TCF OD - Dithranol OD	535	317 to 771	0.8462	0.7997 to 0.8855	16389
Vit D BD - PS OD - Referral	492	293 to 672	0.8440	0.7974 to 0.8837	16388
PS OD - Vit D BD - Referral	484	251 to 680	0.8436	0.7968 to 0.8834	16387
PS OD - TCF OD - Referral	540	244 to 831	0.8456	0.7988 to 0.8853	16371
TCF OD - Vit D BD - Referral	594	399 to 777	0.8481	0.8015 to 0.8875	16369
Vit D BD - TCF OD - Referral	565	375 to 773	0.8464	0.7999 to 0.8859	16362

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @£20k
PS OD - VIt D OD - Referral	526	228 to 764	0.8426	0.7956 to 0.8827	16325
Vit D OD - PS OD - Referral	533	270 to 757	0.8423	0.7954 to 0.8823	16313
Vit D OD - Vit D BD - Referral	554	366 to 721	0.8428	0.7963 to 0.8829	16303
Vit D OD - TCF OD - Referral	611	352 to 867	0.8449	0.7986 to 0.8844	16288
Vehicle only	664	605 to 727	0.8358	0.7887 to 0.8758	16052

(a) Ranked in order of total net monetary benefit at a threshold willingness to pay of £20,000 per QALY gained

Table 14: Disaggregated total costs by items of resource use

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
PS BD - Concurrent - Coal Tar BD	£102	£44	£14	£57	£217
Concurrent - PS BD - Coal tar BD	£112	£43	£14	£57	£226
PS BD - Concurrent - Vit D BD	£112	£44	£14	£57	£227
Concurrent - PS BD - Vit D BD	£121	£43	£14	£57	£235
Concurrent - PS BD - Vit D OD	£125	£45	£16	£68	£254
PS BD - Vit D BD - Concurrent	£126	£46	£14	£57	£243
Concurrent - Vit D BD - PS BD	£144	£45	£14	£57	£260
PS BD - Concurrent - Dithranol OD	£123	£46	£16	£69	£254
Concurrent - PS BD - Dithranol OD	£133	£45	£16	£69	£263
PS BD - Vit D OD - Concurrent	£130	£50	£16	£68	£264
PS OD - PS BD - Coal Tar BD	£95	£55	£19	£80	£249
PS BD - Vit D BD - Coal Tar BD	£133	£49	£17	£70	£269
Vit D BD - PS BD - Concurrent	£142	£48	£14	£57	£261
Concurrent - Vit D BD - Coal Tar BD	£161	£46	£16	£66	£289
PS OD - Concurrent - Coal tar BD	£120	£54	£18	£75	£267
Vit D BD - Concurrent - PS BD	£155	£47	£14	£57	£273
PS OD - PS BD - Vit D BD	£107	£55	£19	£79	£260
Concurrent - Vit D BD - PS OD	£151	£48	£18	£74	£291
PS BD - Vit D BD - TCF OD	£213	£45	£12	£49	£319
PS BD - Vit D OD - Coal Tar BD	£138	£53	£20	£84	£295
PS OD - Concurrent - VIt D BD	£132	£53	£18	£74	£277
Concurrent - Vit D BD - TCF OD	£237	£42	£11	£46	£336
Vit D OD - PS BD - Concurrent	£142	£54	£16	£68	£280
Vit D BD - PS BD - Coal Tar BD	£149	£51	£17	£70	£287
PS BD - Vit D OD - Vit D BD	£151	£53	£20	£83	£307
PS OD - PS BD - Vit D OD	£112	£58	£22	£94	£286
Vit D OD - Concurrent - PS BD	£157	£53	£16	£68	£294
Vit D BD - PS OD - PS BD	£140	£55	£19	£79	£293
PS OD - Vit D BD - PS BD	£134	£57	£19	£79	£289
PS BD - TCF OD - Coal Tar BD	£268	£41	£12	£49	£370
Vit D BD - Concurrent - Coal tar BD	£172	£49	£16	£66	£303

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
Vit D BD - PS OD - Concurrent	£154	£54	£18	£74	£300
PS OD - Vit D BD - Concurrent	£148	£56	£18	£74	£296
Concurrent - TCF OD - Coal tar BD	£289	£39	£11	£46	£385
PS BD - Vit D OD - TCF OD	£232	£48	£14	£58	£352
Vit D BD - PS BD - TCF OD	£230	£46	£12	£49	£337
PS BD - Vit D BD - Dithranol OD	£158	£51	£20	£84	£313
PS OD - PS BD - Dithranol OD	£123	£58	£23	£96	£300
PS BD - TCF OD - Vit D BD	£276	£41	£12	£49	£378
Concurrent - Vit D BD - Dithranol OD	£184	£49	£19	£79	£331
Concurrent - TCF OD - Vit D BD	£297	£39	£11	£46	£393
PS BD - Concurrent - Referral	£128	£48	£28	£126	£330
Concurrent - PS BD - Referral	£137	£47	£28	£126	£338
Vit D OD - PS BD - Coal tar OD	£150	£57	£20	£84	£311
Vit D BD - Concurrent - TCF OD	£249	£45	£11	£46	£351
PS OD - Concurrent - Dithranol OD	£147	£56	£21	£90	£314
PS OD - Vit D OD - PS BD	£137	£62	£22	£94	£315
PS OD - Vit D OD - Concurrent	£153	£61	£21	£88	£323
Vit D OD - Concurrent - Coal tar BD	£176	£55	£19	£78	£328
Vit D OD - PS BD - Vit D BD	£163	£57	£20	£83	£323
Vit D OD - PS OD - PS BD	£140	£62	£22	£94	£318
PS BD - TCF OD - Dithranol OD	£286	£43	£14	£59	£402
PS BD - Vit D OD - Dithranol OD	£167	£56	£23	£100	£346
Vit D BD - PS OD - Coal Tar BD	£163	£58	£22	£92	£335
Vit D BD - PS BD - Dithranol OD	£174	£53	£20	£84	£331
PS OD - Vit D BD - Coal Tar BD	£157	£59	£22	£92	£330
Concurrent - TCF OD - Dithranol OD	£306	£41	£13	£55	£415
Vit D OD - PS OD - Concurrent	£156	£61	£21	£88	£326
Vit D OD - PS BD - TCF OD	£244	£52	£14	£58	£368
TCF OD - PS BD - Coal Tar BD	£356	£38	£12	£49	£455
Vit D OD - Concurrent - Vit D BD	£189	£55	£19	£78	£341
Vit D BD - Concurrent - Dithranol OD	£196	£51	£19	£79	£345
TCF OD - PS BD - Vit D BD	£364	£38	£12	£49	£463
Vit D OD - Concurrent - TCF OD	£265	£51	£13	£54	£383
Vit D OD - Vit D BD - PS BD	£191	£59	£20	£83	£353
Vit D BD - PS OD - TCF OD	£265	£52	£15	£64	£396
PS OD - Vit D BD - TCF OD	£259	£54	£15	£64	£392
Vit D OD - Vit D BD - Concurrent	£205	£58	£19	£78	£360
PS OD - Vit D OD - Coal tar BD	£164	£65	£25	£109	£363
TCF OD - PS BD - Vit D OD	£367	£40	£14	£58	£479
Vit D OD - PS BD - Dithranol OD	£180	£60	£23	£100	£363
TCF OD - Vit D BD - PS BD	£384	£39	£12	£49	£484
Vit D OD - PS OD - Coal tar BD	£167	£65	£25	£109	£366

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
TCF OD - PS BD - Dithranol OD	£374	£40	£14	£59	£487
Vit D BD - TCF OD - PS BD	£341	£44	£12	£49	£446
Vit D OD - Concurrent - Dithranol OD	£204	£58	£22	£94	£378
PS OD - Vit D OD - Vit D BD	£180	£65	£25	£108	£378
PS OD - TCF OD - Coal Tar BD	£322	£50	£16	£64	£452
Concurrent - Vit D BD - Referral	£190	£50	£31	£142	£413
PS BD - Vit D BD - referral	£164	£53	£33	£151	£401
Vit D OD - PS OD - Vit D BD	£183	£65	£25	£108	£381
Vit D BD - PS OD - Dithranol OD	£195	£61	£26	£110	£392
PS OD - Vit D BD - Dithranol OD	£189	£63	£26	£110	£388
PS OD - TCF OD - Vit D BD	£332	£50	£15	£64	£461
TCF OD - Vit D BD - Coal Tar BD	£399	£41	£14	£57	£511
PS BD - TCF OD - Referral	£290	£44	£25	£110	£469
Concurrent - TCF OD - Referral	£310	£42	£23	£103	£478
Vit D OD - Vit D BD - Coal Tar BD	£215	£61	£23	£96	£395
PS OD - Vit D OD - TCF OD	£281	£58	£18	£76	£433
PS OD - PS BD - Referral	£130	£60	£37	£168	£395
PS OD - Concurrent - Referral	£153	£58	£35	£158	£404
Vit D BD - TCF OD - Coal Tar BD	£356	£46	£14	£57	£473
TCF OD - Vit D BD - PS OD	£391	£42	£15	£64	£512
Vit D OD - Vit D BD - PS OD	£202	£63	£25	£108	£398
Vit D OD - PS OD - TCF OD	£284	£59	£18	£76	£437
Vit D OD - TCF OD - PS BD	£366	£50	£14	£58	£488
Vit D BD - PS BD - Referral	£180	£55	£33	£151	£419
Vit D BD - Concurrent - Referral	£202	£53	£31	£142	£428
Vit D OD - Vit D BD - TCF OD	£320	£56	£16	£67	£459
PS OD - TCF OD - Dithranol OD	£345	£52	£18	£77	£492
PS BD - Vit D OD - Referral	£174	£58	£38	£174	£444
PS OD - Vit D OD - Dithranol OD	£201	£69	£30	£130	£430
TCF OD - Vit D BD - Dithranol OD	£420	£43	£16	£68	£547
TCF OD - PS BD - Referral	£378	£41	£25	£110	£554
Vit D OD - PS OD - Dithranol OD	£204	£69	£30	£130	£433
Vit D BD - TCF OD - Dithranol OD	£377	£48	£16	£68	£509
Vit D OD - TCF OD - Coal Tar BD	£384	£51	£16	£67	£518
Vit D OD - Vit D BD - Dithranol OD	£248	£65	£27	£115	£455
Vit D OD - TCF OD - Vit D BD	£394	£51	£16	£67	£528
Vit D OD - PS BD - Referral	£187	£62	£38	£174	£461
Vit D OD - Concurrent - Referral	£211	£60	£36	£164	£471
Vit D OD - TCF OD - Dithranol OD	£408	£54	£19	£81	£562
Vit D BD - PS OD - Referral	£203	£64	£41	£189	£497
PS OD - Vit D BD - Referral	£197	£65	£41	£189	£492
PS OD - TCF OD - Referral	£350	£54	£31	£139	£574

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
TCF OD - Vit D BD - Referral	£424	£44	£28	£124	£620
Vit D BD - TCF OD - Referral	£381	£49	£28	£124	£582
PS OD - Vit D OD - Referral	£211	£72	£47	£217	£547
Vit D OD - PS OD - Referral	£214	£72	£47	£217	£550
Vit D OD - Vit D BD - Referral	£256	£67	£42	£195	£560
Vit D OD - TCF OD - Referral	£413	£56	£32	£144	£645
Vehicle only	£178	£117	£63	£309	£667

(a) Disaggregated costs estimated from the deterministic analysis and as such may not match the probabilistic mean total costs exactly

M.3.2 Sensitivity analyses

A series of sensitivity analyses suggested that the conclusions from the base case are somewhat sensitive to changes in some parameters and/or assumptions.

M.3.2.1 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 this sensitivity analysis are presented in Table 15.

Table 15: Incremental analysis of sensitivity analysis using patient-reported outcome (PAGI)

Strategy (a)	Cost	Incremental Cost	Benefit (QALYs)	Incremental benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold (b)
PS OD - Concurrent - Vit D BD	£275.50		0.8477			£16,679	31%
Concurrent - Vit D BD - PS OD	£305.00	£29.50	0.8481	0.0004	£73,750	£16,657	6%
Concurrent - Vit D BD - TCF OD	£370.50	£65.50	0.8487	0.0006	£109,167	£16,604	2%
Concurrent - TCF OD - Vit D BD	£410.80	£40.30	0.849	0.0003	£134,333	£16,569	0%
TCF OD - Vit D BD - PS OD	£487.40	£76.60	0.8491	1E-04	£766,000	£16,495	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 Concurrent – PS BD – Vit D BD (optimal in 20% of simulations)

Results of the analysis using patient reported outcomes indicates that starting treatment with once daily potent corticosteroids, moving on 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 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 betamethasone dipropionate and calcipotriol monohydrate, 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 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 coal tar represents the better third line treatment option.

M.3.2.2 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[3] 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 betamethasone dipropionate and calcipotriol monohydrate increased to over £787,000 compared to starting with concurrent treatment (£174,500 in the base case).

M.3.2.3 4-week quantity of combined product containing betamethasone dipropionate and calcipotriol monohydrate

In the base case, hypothetical patients are assumed to use 134.0 g of combined product containing betamethasone dipropionate and calcipotriol monohydrate 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 betamethasone dipropionate and calcipotriol monohydrate 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 betamethasone dipropionate and calcipotriol monohydrate 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 is still more likely to be considered cost-effective.

M.3.2.4 Sensitivity analyses – Restricted comparators

The base case analysis put a several conditions on the way topicals could be sequenced (see Table 1 in section Table 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 (combined product containing betamethasone dipropionate and calcipotriol monohydrate) 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 betamethasone dipropionate and calcipotriol monohydrate 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 concurrently 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 betamethasone dipropionate and calcipotriol monohydrate 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, 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 betamethasone dipropionate and calcipotriol monohydrate 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 betamethasone dipropionate and calcipotriol monohydrate 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 alone and then twice daily coal tar. Combined product containing betamethasone dipropionate and calcipotriol monohydrate 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.

M.3.2.5 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 betamethasone dipropionate and calcipotriol monohydrate 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 betamethasone dipropionate and calcipotriol monohydrate 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 betamethasone dipropionate and calcipotriol monohydrate 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 betamethasone dipropionate and calcipotriol monohydrate 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 and potent corticosteroids becomes more cost-effective than starting with potent corticosteroids alone. When the time horizon is extended, combined product containing betamethasone dipropionate and calcipotriol monohydrate 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.

M.4 Discussion

M.4.1 Summary of results

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 of 122 compared sequences, the analysis suggests that initial treatment with potent corticosteroids followed by concurrent treatment with potent corticosteroid and vitamin D or vitamin D analogue (morning/evening application) 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 betamethasone dipropionate and calcipotriol monohydrate should be offered third in the sequence, after potent corticosteroids and concurrent treatment

Sequences starting with once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate were slightly more effective than the same sequence starting with

concurrent potent corticosteroid and vitamin D or vitamin D analogue; 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.

M.4.2 Limitations & interpretation

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 betamethasone dipropionate and calcipotriol monohydrate 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 aware 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.

The analysis specifically found twice daily potent corticosteroid to be highly cost-effective, but the GDG expressed concern that the well known side effects of potent corticosteroids (e.g. skin atrophy, rapid relapse) were not adequately captured in the economic model owing to a lack of data. Twice daily potent corticosteroids came out more cost-effective than once daily, largely because the quantities of topical used for once and twice daily application were very similar, yet the network meta-analysis showed a non-significant trend toward twice daily being more effective in the investigator assessed outcomes used in the base case (OR=1.833, 95% CrI 0.46 to 7.985). However, this trend is reversed for the patient assessed outcome – twice daily performed less well than once daily (OR=0.714, 95% CrI 0.14 to 3.549). This finding is reflected in the results of this sensitivity analysis where patient reported response was used, which show once daily to be more cost-effective than twice daily. The consensus of the GDG was that they could not be certain that twice daily potent corticosteroids were more effective than once daily potent corticosteroids. They concluded that even if twice daily application was more effective at inducing clearance or near clearance than once daily application, the risks of higher dose steroids were very likely to outweigh the potential benefits and make the intervention comparatively less effective and cost-effective. Therefore the GDG excluded strategies that included twice daily corticosteroids in the first two lines of 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. In order to avoid continuous treatment with steroids for more than 8 weeks the GDG also chose to exclude strategies that contained

corticosteroids in two consecutive lines of treatment. After these considerations the most cost-effective strategy was:

- 1st line – Concurrent treatment with potent corticosteroid and vitamin D or vitamin D analogue (morning/evening application)
- 2nd line – twice daily vitamin D or vitamin D analogue
- 3rd line – twice daily potent corticosteroid

The GDG specifically considered whether they should offer concurrent treatment (morning/evening) with two separate topicals or offer combined treatment in a single product for use just once daily. They considered the results of the cost-effectiveness analysis which showed that combined treatment (once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate) is not cost-effective compared with concurrent treatment. This is because the network meta-analysis found them to have similar efficacy, but combined product containing betamethasone dipropionate and calcipotriol monohydrate is much more costly (unit cost of 120 g combined product containing calcipotriol monohydrate and betamethasone dipropionate is between 2 and 4 times more costly than combined unit cost of 100 g of vitamin D analogue and potent corticosteroid each). The GDG did not think that the combined formulation product as first-line treatment produced enough additional benefit to justify its substantial additional cost.

The base case cost-effectiveness analysis 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 potent corticosteroid , twice daily coal tar, or once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate was likely to be most cost effective. To reflect the uncertainties in the conclusions about cost-effectiveness and provide prescribers and patients with a degree of choice, the GDG chose to recommend all of these interventions if the patient has failed to achieve clearance or near clearance with concurrent treatment with potent corticosteroid and vitamin D or vitamin D analogue (morning/evening application followed by a course of twice daily vitamin D or vitamin D analogue. They considered that some people may not choose to use coal tar as it has a pungent odour and that some people may prefer vitamin D or vitamin D analogues as they are generally safe for long term use. They considered that the combined potent corticosteroid and vitamin D analogue product was much more costly than other alternatives, but it may represent value for NHS resource in a select group of patients with resistant mild to moderate psoriasis. It also may be more cost-effective to offer if the alternative is referral and escalation of treatment to much costlier interventions (e.g. phototherapy, specialist applied topicals, systemic therapy, biologic therapy).

The NCGC cost-effectiveness did not find short contact dithranol to be more cost-effective than other first, second and third line alternatives in the base case or any sensitivity analyses. The GDG did not want to rule dithranol out as a treatment option for some patients, but considered it only potentially cost-effective for patients who have failed to respond to other more efficacious and easy-to-use topical therapies. They emphasised the need for health care professional to clearly explain proper application of dithranol for home use in order to maximise its effectiveness and reduce the inconvenience. They also considered that dithranol may be best delivered as part of treatment in a day care setting with specialist nurse supervision.

The cost-effectiveness of very potent corticosteroids was not evaluated as part of the NCGC decision modelling as the GDG did not consider it to represent a safe treatment option for the management of mild to moderate psoriasis being managed in primary care. They considered that based on its efficacy and relatively low cost (100 g cream or ointment = £7.90), it was likely to represent good value for NHS resource so long as it is used with caution and under careful supervision of a specialist in secondary care.

In thinking about the potential risks of prescribing potent, and in select cases very potent corticosteroids, the GDG considered it essential to build in monitoring to assess efficacy and adverse

events. The time horizon of the economic model was too short (1 year) to explicitly consider annual monitoring in the long term; however, it is very likely that the extra cost of an annual GP or specialist visit would be offset by the avoidance of irreversible adverse events that are associated with inappropriate and unsafe use of corticosteroids.

The cost-effectiveness of topical treatments for children was not explicitly considered in the decision modelling undertaken for the guideline; however, the GDG considered the results broadly applicable to this population. They considered that once daily applications in children were likely to be more appropriate and that evidence of effectiveness for combination strategies are lacking. Therefore, they concluded that for children with mild to moderate psoriasis, once daily application of potent corticosteroids or vitamin D or vitamin D analogue were likely to represent the best value for NHS resource. They also considered how infrequent psoriasis occurs in children and that referral to secondary care may be justified.

M.4.3 Generalisability to other populations / settings

The analysis may be most applicable to patients with newly identified mild to moderate psoriasis, but the results may also be applicable to patients for whom topical therapy may be offered in addition to other therapies, such as phototherapy, systemic therapy or biologic therapy. These patients are likely to have much more widespread and/or severe disease and therefore topical therapy alone is likely to be insufficient and even inappropriate. However, the conclusion that topical corticosteroids offer good value for NHS resource and offer better value when combined with vitamin D analogue than combined product containing betamethasone dipropionate and calcipotriol monohydrate is likely to apply to any population requiring topical therapies.

M.4.4 Comparisons 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[3]. Bottomley and colleagues found 8 weeks of once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate 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. 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 combined product containing betamethasone dipropionate and calcipotriol monohydrate 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 combined product containing betamethasone dipropionate and calcipotriol monohydrate (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 combined product containing betamethasone dipropionate and calcipotriol monohydrate costs £29.26 more than Bottomley and colleagues did. Furthermore, the difference between combined product containing betamethasone dipropionate and calcipotriol monohydrate and concurrent treatment is different between the analyses. The additional cost of combined product containing betamethasone dipropionate and calcipotriol monohydrate 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 combined product

containing betamethasone dipropionate and calcipotriol monohydrate used by Bottomley and colleagues (i.e. 92.6 g, £61.27). The ICER for combined product containing betamethasone dipropionate and calcipotriol monohydrate 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.'

M.4.5 Conclusion

- 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 (morning/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 betamethasone dipropionate and calcipotriol monohydrate was likely to be most cost effective.

M.4.6 Implications for future research

Research into the longer term effectiveness and safety of available topical therapies would be valuable for future economic analyses undertaken in this area. In addition, it would be useful to identify the resource use associated with safe and effective methods of self-management with topicals, as there is quite a large degree of uncertainty about what 'maintenance' therapy actually means in the context of clinical practice.

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