Appendix N: Cost-effectiveness analysis – Topical therapies for the treatment of scalp psoriasis

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N.1 Introduction

The review of clinical evidence for topical therapies used in the treatment of individuals with mild to moderate scalp psoriasis showed that there were several treatment options – tars, corticosteroids (potent and very potent), vitamin D or vitamin D analogues and combination products – each associated with certain advantages and disadvantages. The results of the network meta-analysis indicated that some interventions, such as very potent corticosteroid as well as combined 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.

One cost-effectiveness analysis was identified in the published literature, but it had methodological limitations that called its conclusions into question. The analysis by Affleck[1] did not include all of the relevant comparators under consideration for the guideline, namely very potent corticosteroids. Furthermore, the treatment effects used in their analysis differed from those found in the NCGC clinical review and network meta-analysis, and this difference was considered likely to affect the conclusion of the analysis.

Due to 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 for scalp psoriasis 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.

N.2 Methods

N.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 scalp 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.

N.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 specialist applied topicals 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: Possible sequences of first, second and third line treatment

First line	Second line	Third line
Vitamin D or vitamin D analogue OD	Vitamin D or vitamin D analogue OD	Combined OD
Vitamin D or vitamin D analogue BD	Vitamin D or vitamin D analogue BD	Concurrent am/pm
Potent corticosteroid OD	Potent corticosteroid OD	Very potent corticosteroid OD
Potent corticosteroid BD	Potent corticosteroid BD	Very potent corticosteroid BD
Combined OD	Combined OD	Coal tar polytherapy (Capasal)
Concurrent am/pm	Concurrent am/pm	Referral to specialist
Very potent corticosteroid OD	Very potent corticosteroid OD	
Very potent corticosteroid BD	Very potent corticosteroid BD	

The following conditions were placed on the sequences, ensuring that they represented logical clinical practice:

- Once daily treatment with a given topical would not come after a failure of twice daily treatment with the same topical;
- Once daily treatment with potent corticosteroid or vitamin D or vitamin D analogue would not come after once daily two-compound formulation product
- Once or twice daily treatment with potent corticosteroid would not come after once or twice daily with very potent corticosteroid

Most comparators focus on evaluating a trial of three different treatments before referral for specialist review, but the GDG was also interested in whether earlier escalation of care might be more cost-effective. To test this, strategies have also been combined into two-treatment sequences with referral following a failure of second line treatment.

Due to the unacceptability coal tar as a routine treatment (strong and unpleasant odours), this treatment was reserved for third line treatment only. This reflects their current placement in primary care given the availability of more acceptable and effective topicals such as those being compared as first and second line topicals.

N.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 scalp psoriasis.

N.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.

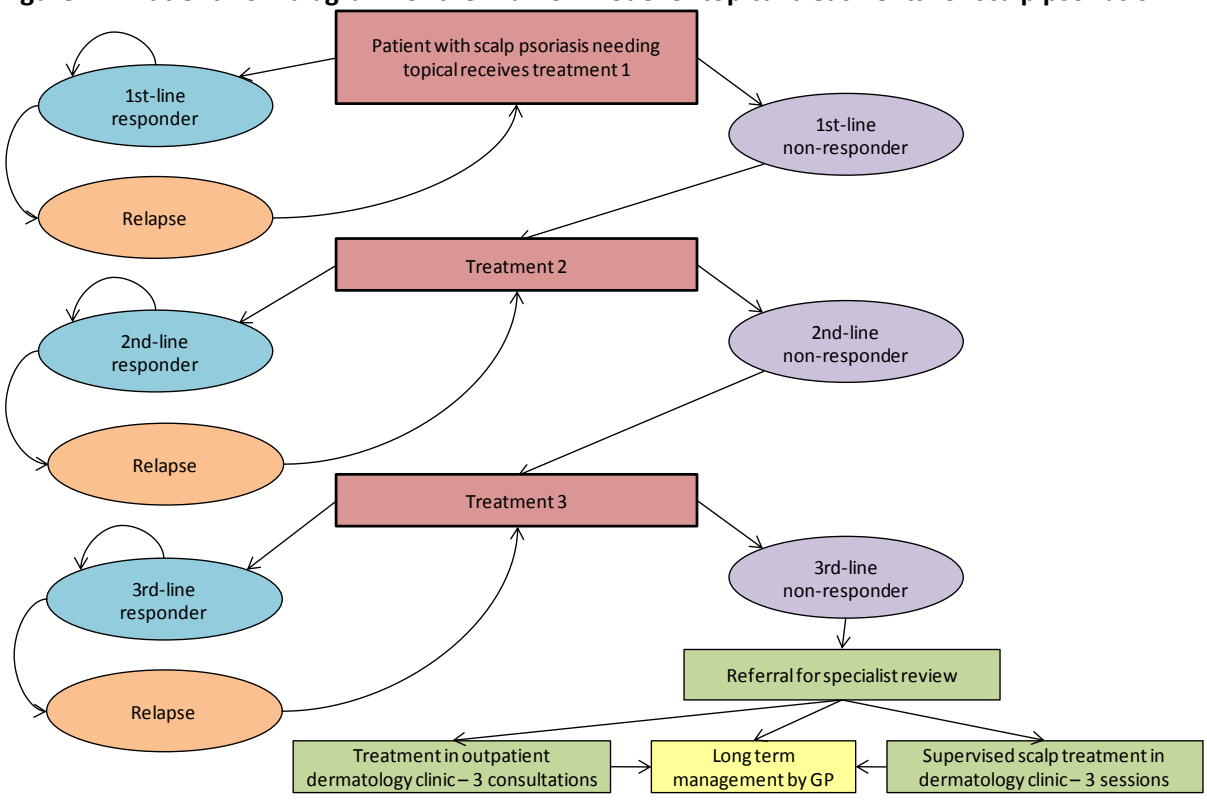
N.2.2 Approach to modelling

N.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 Affleck and colleagues[1] 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: Patient flow diagram for the Markov model of topical treatments for scalp psoriasis



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 scalp psoriasis) or no response (defined as something less than clearance/near clearance of their scalp 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 after 8 weeks (or 4 weeks in the case of very potent corticosteroids) 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. Another group of those referred will be treated over 3 appointments in outpatient dermatology and some will undergo supervised scalp treatment with intensive topical therapy over the course of 3 outpatient dermatology appointments. Following referral and management in the specialist setting, they will be managed by their GP with 3-monthly appointments.

N.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.

N.2.3 Model inputs

N.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 scalp psoriasis	
Perspective	UK NHS and & PSS	NICE reference case[2]
Time horizon	1 year	
Discounting	Not applicable (a)	

(a) 3.5% annual discounting applied to costs and benefits in sensitivity analyses extending time horizon beyond 1 year

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	11.3%	Beta: α= 42; β= 331	95% CI: 8.1% to 14.5% Network meta-analysis (see Appendix L)
Efficacy (Odds ratio compared to Baseline)			
Vitamin D or vitamin D analogue OD	6.464	10,000 simulated odds ratios from the NMA were used	Network meta-analysis (see Appendix L)
Vitamin D or vitamin D analogue BD	4.329		Network meta-analysis (see Appendix L)
Potent corticosteroid OD	17.60		Network meta-analysis (see Appendix L)
Potent corticosteroid BD	7.908		Network meta-analysis (see Appendix L)
Very potent corticosteroid OD	11.28		Network meta-analysis (see Appendix L)
Very potent corticosteroid BD	28.28		Network meta-analysis (see Appendix L)
TCF product OD	21.01		Network meta-analysis (see Appendix L)
Coal tar polytherapy	1.909		Network meta-analysis (see Appendix L)
Relapse			
All topical therapies	35.5%	Beta: α=192; β= 137	Assumption; test range in sensitivity analysis
Probability of specialist referral and subsequent management			
Referral for specialist review	100%		Assumption
Specialist topicals advice and management by GP	50%		Assumption
Topicals with specialist advice and follow-up	25%		Assumption
Intensive scalp treatment in outpatient day care	25%		Assumption
Probability of response to Intensive scalp treatment	75%		Assumption
Health-related Quality of Life (a)			
Response – Clear/nearly clear	0.7962	Normal: mean = 0.2038 sd = 0.007	Affleck 2011[1]
Non-response – Not clear/nearly clear	0.7781	Normal: mean = 0.0181 sd = 0.009	Affleck 2011[1]
Baseline	0.7670	Normal: mean = 0.0111	Affleck 2011[1]

Parameter description	Point estimate	Probability distribution	Source/notes
		sd = 0.009	
Resource use			
4 weeks of topical treatment			
Vehicle BD	77.6 g	Gamma: α=25.23 β=3.08	Data only available for once daily from Jemec 2008[3], Jemec 2011[4], Tyring 2010[5]
Vitamin D or vitamin D analogue OD	89.2 g	Gamma: α=238.64 β=0.37	Jemec 2008[3], Jemec 2011[4], van de Kerkhof 2009[6]
Vitamin D or vitamin D analogue BD	85.6 g	Gamma: α=38.06 β=2.25	Affleck 2011[1]
Potent corticosteroid OD	87.35 g	Gamma: α=173.49 β=0.50	Buckley 2008[7], Jemec 2008[3], Jemec 2011[4], van de Kerkhof 2009[6]
Potent corticosteroid BD	90.16 g	Gamma: α=184.82 β=0.49	
Very potent corticosteroid OD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
Very potent corticosteroid BD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
Combined vitamin D and potent corticosteroid OD	71.4 g	Gamma: α=127.25 β=0.56	Buckley 2008[7], Jemec 2008[3], Jemec 2011[4], Tyring 2010[5], van de Kerkhof 2009[6]
Coal tar polytherapy	250 mL	Gamma: α=25.00 β=10.00	assumption
Health care consultations			
GP consultations following non-response to topical treatment	1 per treatment change		Assumption
Specialist outpatient consultation	1 following failure of 3 topicals		Assumption
Specialist follow-up and support	3 additional outpatient visits		Assumption
Intensive scalp treatment in outpatient day care	3 visits (at 1, 3 and 6 months)		Assumption
Long term management by GP	1 visit per 3 months		Assumption
Cost (£)			
Unit cost of topical treatment			

Parameter description	Point estimate	Probability distribution	Source/notes
Vehicle	500g = £5.83		Doublebase gel
Vitamin D	60 g = £12.70; 120 g = £26.07		Calcipotriol scalp solution
Potent corticosteroid	100 g = £3.75		Betacap scalp application
Very potent corticosteroid	100 g = £10.42; 30 g = £3.07		Dermovate scalp application
Combined vitamin D and potent corticosteroid	60 g = £36.50; 120 g = £67.79		Dovobet gel
Coal Tar	250 g = £4.69		Capasal shampoo
Unit cost of healthcare consultations			
GP consultation	£28		PSSRU 2010[8]
Specialist outpatient consultation	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[9]
Specialist outpatient nurse consultation (first visit)	£81	lognormal: log of mean = 4.40 se of logs = 0.03	NHS Reference costs 2009-10[9]
Specialist outpatient nurse consultation (follow-up visit)	£64	lognormal: log of mean = 4.15 se of logs = 0.05	NHS Reference costs 2009-10[9]
Intensive scalp treatment (JD02C)	£351	lognormal: log of mean = 5.86 se of logs = 0.05	NHS Reference costs 2009-10[9]

(a) See section for more details on how utilities were parameterised in the model

N.2.3.2 Baseline event rates

Creams and emollients with no active ingredient are a typical first-line therapy for patients presenting with scalp 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

scalp therapies and dividing by the aggregate sample size from the same arms. This resulted in a probability of 11.3% (95% CI: 8.1% to 14.5%) for achieving clear/nearly clear. For the probabilistic analysis, uncertainty in the risk parameter for vehicle/placebo was incorporated using a beta distribution (α=42; β=331).

N.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 of scalp treatment (see Appendix L) were applied to the baseline probabilities outlined above. The only estimates available and therefore used relate to the investigator assessed outcome (IAGI/PGA). The odds ratios used in the analysis are presented in Table 4.

Table 4: Relative treatment effects from NMA

Intervention	Odds ratio (95% CI) vs placebo
Vitamin D or vitamin D analogue OD	6.464 (1.202 to 50.7)
Vitamin D or vitamin D analogue BD	4.329 (1.43 to 16.4)
Potent corticosteroid OD	17.60 (3.539 to 148.0)
Potent corticosteroid BD	7.908 (2.681 to 24.2)
Very potent corticosteroid OD	11.28 (2.278 to 72.1)
Very potent corticosteroid BD	28.28 (13.34 to 68.3)
Combined vitamin D and potent corticosteroid OD	21.01 (4.396 to 128.0)
Coal tar polytherapy	1.909 (0.412 to 11.5)

(a) <Insert Note here>

To calculate the absolute probability of response to a given topical treatment (presented in Table 5), the odds ratios of that intervention compared to twice daily placebo from the network meta-analysis was converted into a relative risk and applied to the 11.1% 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.

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

Intervention	Probabilities of response
Vehicle BD	11.26%
Vitamin D or vitamin D analogue OD	45.06%
Vitamin D or vitamin D analogue BD	35.45%
Potent corticosteroid OD	69.07%
Potent corticosteroid BD	50.09%
Very potent corticosteroid OD	58.87%

Intervention	Probabilities of response
Very potent corticosteroid BD	78.21%
TCF OD	72.72%
Coal Tar polytherapy	19.50%

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 vs late response

The data used to estimate the overall probabilities of response to treatment (Table 5) were based on trials of varying duration, 2 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. This applies to all topicals except for very potent corticosteroids, which for reasons of safety are assumed to be trialled for a maximum of 4 weeks.

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 only available from three studies[3,6,10]. These studies reported response rates at 4 weeks and 8 weeks for vehicle, potent corticosteroid, vitamin D or vitamin D analogue and two-compound formulation product.

The data showed that more than half of all responders at 8 weeks had responded fully by 4 weeks across all topicals, including vehicle alone. The data from the three trials was broadly similar for each topical and therefore the probabilities of response at 4 weeks versus 8 weeks were estimated by calculating a weighted average across the studies.

The weighted average proportion of early (0 to 4 weeks) and late (5 to 8 weeks) responders from the studies 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)
Vehicle	11.26%	65%	7.3%	4.31%
Vitamin D or vitamin D analogue OD	45.06%	61%	27.6%	24.15%

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)
Vitamin D or vitamin D analogue BD	35.45%	61%	21.7%	17.57%
Potent corticosteroid OD	69.07%	85%	58.4%	25.64%
Potent corticosteroid BD	50.09%	85%	42.4%	13.42%
Very potent corticosteroid OD	58.87%	100%	58.87%	NA
Very potent corticosteroid BD	78.21%	100%	78.21%	NA
TCF OD	72.72%	87%	62.9%	26.39%
Coal Tar polytherapy OD	19.50%	50%	9.7%	10.80%

There was no trial data to inform the early compared to late responses for coal tar polytherapy. In the absence of data, the GDG made the assumption that the early versus late breakdown for coal tar polytherapy was 50/50, the same as the breakdown assumed in the analysis of topicals used in the economic evaluation of topicals for the trunks and/or limbs (see Appendix M).

N.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 affecting the scalp. As in the analysis for topicals used in all sites, the RCT data with regard to relapse was sparse for the same reasons: 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 equal to the probability used in the analysis of all sites; that is 5.5% for all interventions. Average risk of relapse at 8 weeks follow-up across the trials of chronic plaque psoriasis of all sites 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.

N.2.3.5 Referral and specialist management

All hypothetical patients who fail to respond to their third topical therapy are assumed to be referred for specialist review. This figure, which is higher than the 60 percent assumed in the model for the treatment of trunk and limbs, is based on GDG opinion.

Among those patients who are referred onward for consultation with a specialist, 50 percent will be given specialist advice and support about how to better manage their scalp psoriasis with topical therapies. In the GDG's experience, a large proportion of patients who are referred to secondary care to not need more aggressive treatments and that topical therapy is likely to offer them the best balance of efficacy and safety. The goal at this point in the care pathway is to ensure patients know how and when to use topicals in order to maximise their efficacy.

A further 25 percent of referred patients will be managed by a specialist in outpatient care for a further 3 consultations (after 1, 3 and 6 months). During this time they will undergo topical therapy, but with the additional follow-ups from a specialist, after which they are discarged back to their GP for long term management.

A final 25 percent are offered intensive scalp treatment over 3 days in an outpatient day care centre. This type of treatment involves the use of special topicals with a great deal of specialist supervision. There was no clinical evidence on the efficacy of such treatments for the scalp, therefore the GDG came up with a figure of 75% based on their clinical experience.

N.2.3.6 Utilities

Achievement of clearance or near clearance and associated utility gain was used in the model to determine the impact of scalp psoriasis treatment on overall health. Estimates of utility gain were taken from a recent cost-utility analysis included in the health economic review[1]. The mean utility at baseline was 0.767 and mean utility gain associated with clearance/near clearance was 0.0292. 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 of 0.0111. It is assumed that patients who fail to respond and ultimately reach the point of requiring referral to a specialist return to their baseline level of utility (0.767).

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

Parameter description	Health state utility	Utility gain compared to baseline	Probability distribution (a)	Source/notes
Response: clear/nearly clear	0.7962	0.0292	Normal: mean = 0.2038 sd = 0.007 (b)	Affleck 2011[1]
Non-response: Not clear/nearly clear	0.7781	0.0111	Normal: mean = 0.0181 sd = 0.009 (c)	Affleck 2011[1]
Baseline	0.7670		Normal: mean = 0.0111 sd = 0.009 (d)	Affleck 2011[1]

(a) Utility gains were built into the model using normal 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 = 0.2038, which was subtracted from perfect health (1.0-0.2038=0.7962)
(c) Distribution mean = 0.0181, which was subtracted from response (0.7962-0.0181=0.7781)
(d) Distribution mean = 0.0111, which was subtracted from non-response (0.7781-0.0111=0.7670)

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 (0.0181) 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 (0.767).
- Patients managed long-term by either a GP or a specialist accrue the gain associated with non-responders.

N.2.3.7 Resource use and cost

Topical therapy

Resource use of alternative scalp treatments was based on reported mean quantities of study drugs used by patients in the RCTs[3-7,11] at the end of trial treatment periods. Mean quantities and distribution parameters for the probabilistic analysis are presented in Table 8.

The only estimates available for placebo/vehicle related to once daily application, whereas the model includes twice daily application. In the absence of data, the GDG assumed that these values were broadly similar, accepting that the once daily resource use might be a slight underestimation.

No estimates were available to inform the mean usage of twice daily vitamin D or vitamin D analogue. In the cost-utility analysis by Affleck and colleagues[1], they estimated 4-week mean usage for this strategy to be 85.57 g (95% CI: 58.94-112.2) based on an unpublished trial held on file. We have taken this estimate for use in our model.

No estimate from an RCT was available to inform the mean quantities of once or twice daily very potent corticosteroids or coal tar polytherapy. In the absence of estimates for very potent corticosteroids, we assumed resource use would match the maximum suitable quantities of corticosteroid preparations for the scalp from the BNF: 60 g over 4 weeks. This was assumed to be equal for once and twice daily application. For coal tar polytherapy, the GDG estimated that a patient would use one 250 mL bottle of Capasal per 4-week period.

Unit costs of topicals (Table 9) were taken from the most recent BNF[12]. 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 scalp formulation of each 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	77.6 g	Gamma: α=25.23 β=3.08	Data only available for once daily from Jemec 2008[3], Jemec 2011[4], Tyring 2010[5]
Vitamin D or vitamin D analogue OD	89.2 g	Gamma: α=238.64 β=0.37	Jemec 2008[3], Jemec 2011[4], van de Kerkhof 2009[6]
Vitamin D or vitamin D analogue BD	85.6 g	Gamma: α=38.06 β=2.25	Affleck 2011[1]
Potent corticosteroid OD	87.35 g	Gamma: α=173.49 β=0.50	Buckley 2008[7], Jemec 2008[3], Jemec 2011[4], van de Kerkhof 2009[6]
Potent corticosteroid BD	90.16 g	Gamma: α=184.82 β=0.49	
Very potent corticosteroid OD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF

Topical therapy	Mean quantity used	Probability distribution	Source/notes
Very potent corticosteroid BD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
TCF OD	71.4 g	Gamma: α=127.25 β=0.56	Buckley 2008[7], Jemec 2008[3], Jemec 2011[4], Tyring 2010[5], van de Kerkhof 2009[6]
Coal tar polytherapy	250 mL	Gamma: α=25.00 β=10.00	Assumption

Table 9: Unit costs of topical therapies for scalp psoriasis

Topical therapy	Unit cost (£)	Source/notes
Vehicle	500g = £5.83	Doublebase gel
Vitamin D	60 g = £12.70; 120 g = £26.07	Calcipotriol scalp solution
Potent corticosteroid	100 g = £3.75	Betacap scalp application
Very potent corticosteroid	100 g = £10.42; 30 g = £3.07	Dermovate scalp application
TCF product	60 g = £36.50; 120 g = £67.79 (a)	Dovobet gel; 120 g comes as 2*60 g
Coal Tar polytherapy	250 g = £4.69	Capasal shampoo

*(a) 120 g comes as 2*60 g packs*

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 once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate was 71.4 g. The cheapest combination of packs needed to provide this quantity was one 120 g pack. The 4-week costs of topical treatments 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 of the means reported in the RCTs and its standard error. No mean or standard error was available for very potent corticosteroids or coal tar polytherapy, so the standard error was assumed to be 20% of the assumed 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 once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate was 47 g, then the cheapest combination would be automatically be calculated as one 60 g pack. Similarly, if the sampled value was 153 g, then the cheapest combination would be one 120 g pack and 1 60 g pack.

A different costing method was used for twice daily vehicle. Because the vehicle gel 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	£0.90
Vitamin D or vitamin D analogue OD	£25.40
Vitamin D or vitamin D analogue BD	£25.40

Topical strategy	4-week cost
Potent corticosteroid OD	£3.75
Potent corticosteroid BD	£3.75
Very potent corticosteroid OD	£6.14
Very potent corticosteroid BD	£6.14
TCF product OD	£67.79
Coal Tar polytherapy	£4.69

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.

All 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 (£17.88).

Each patient is seen by a consultant dermatologist in an outpatient clinic, thus accruing this cost. Based on GDG experience, it was assumed that 50% 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. 25% of these patients will be seen in the outpatient clinic by a non-consultant for a further three follow-up visits (1, 3 and 6 months) and then discharged back to long term care with their GP. The remaining 25% of patients is referred for intensive supervised scalp treatment with topicals and accrues the cost of 3 outpatient day care centre sessions. If they respond to this intensive treatment, they are discharged and managed by their GP with 3-monthly appointments. If they do not respond adequately, then they are assumed to be managed in long-term specialist care.

Table 11: Unit cost of health care consultations

Type of healthcare consultation	Health care resource use	Unit cost per consultation	Probability distribution	Source/notes
GP consultations following non-response to topical treatment	• 1 per treatment change • 1 visit per 3 months for long term management	£28		PSSRU 2010[8]
Specialist outpatient consultation (consultant)	• 1 following failure of 3 topicals	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[9]
Specialist follow-up and support (specialist nurse)	• 3 additional outpatient visits	£64	lognormal: log of mean = 4.15 se of logs = 0.05	NHS Reference costs 2009-10[9]
Intensive scalp treatment in outpatient day	• 3 visits (at 1, 3 and 6 months)	£351	lognormal: log of mean = 5.86 se of logs = 0.05	NHS Reference costs 2009-10 (JD02C)[9]

Type of healthcare consultation	Health care resource use	Unit cost per consultation	Probability distribution	Source/notes
care				

N.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.

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

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, optimal 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.

N.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 the first sensitivity analysis, 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 Affleck and colleagues[1]. Also, alternative assumptions about the comparators were used to explore what might be appropriate if there were concerns about safety or contraindications.

N.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 many of the model calculations.

N.3 Results

N.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 once daily potent corticosteroid and then escalating to twice daily very potent corticosteroid and then trying once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate if steroids alone are insufficient to induce clearance or near clearance. This conclusion was based on the comparison of mean costs and mean QALYs across 169 modelled sequences. Base case results for non-dominated and non-extendedly dominated strategies are presented in Table 12.

By starting with twice daily very potent corticosteroid and moving on to once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate and then ultimately twice daily vitamin D or vitamin D analogue, 0.0004 QALYs could be gained, but for an additional £102 per year. This gives and ICER of £254,250 per QALY gained, which is not cost-effective at the NICE threshold.

Table 12: Incremental analysis of base case results – scalp psoriasis

Strategy (a)	Cost	Incrmntl Cost	Benefit (QALYs)	Incrmntl benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold (b)

Strategy (a)	Cost	Incrmntl Cost	Benefit (QALYs)	Incrmntl benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold (b)
PS OD - PS BD - VPS BD	£145		0.77407			£15,337	18%
PS OD - VPS BD - TCF OD	£156	£11	0.77486	0.00079	£14,430	£15,341	40%
VPS BD - TCF OD - Vit D BD	£258	£102	0.77526	0.0004	£254,250	£15,247	0%

(a) All sequences not presented here were ruled out through dominance (more costly and less effective than a strategy included in the table) or extended dominance (more costly and less effective than a mixture of two other strategies included in the table)

(b) Strategies not on the cost-effectiveness frontier but with second, fourth and fifth highest expected net benefits include PS OD – VPS OD – VPS BD, PS OD –V PS BD – Vit D OD and PS OD – VPS BD –Vit D BD, respectively.

Mean costs and QALYs and their respective 95% confidence intervals for all 169 strategies, ranked in order of mean net benefits at £20,000 per QALY threshold, are presented in Table 13. These show that the most effective (and cost-effective) strategies involved use of potent and very potent corticosteroids in all three lines of treatment. Results also showed that a strategy of using vehicle gel or emollient with no active agent only was the most costly and least effective strategy, largely driven by the cost of referrals and specialist management for non-responders. Similarly, a strategy of prescribing coal tar polytherapy for ongoing management was only slightly more effective than continued use of vehicle gel and cost the third most of any treatment sequence. Strategies that included once or twice daily vitamin D or vitamin D analogue were not cost-effective regardless of where they came in a treatment sequence. This finding is driven by their relatively low rank in terms of effectiveness and their relatively high acquisition cost relative to potent and very potent corticosteroids. Two compound formulation product, although second most effective in the network meta-analysis, was not found to be cost-effective as a first, second or third line intervention. Like vitamin D or vitamin D analogues, its high unit cost compared to other cheaper and effective topicals makes it unlikely to represent reasonable value for NHS resources.

A breakdown of total costs by type of resource use (i.e. topicals, GP visits, outpatient consultations, day centre treatments) is presented for all modelled strategies in table 14. Based on this disaggregation, it becomes clear that strategies with combined product containing betamethasone dipropionate and calcipotriol monohydrate have relatively high topical costs, some of which are offset by reduced downstream costs in terms of consultations with specialists and intensive treatment in a day care centre setting. The earlier that combined product containing betamethasone dipropionate and calcipotriol monohydrate appears in the treatment sequence, the greater the proportion of total costs can be attributed to the topical itself. Strategies with potent and very potent corticosteroids show similar downstream costs as strategies involving combined product containing betamethasone dipropionate and calcipotriol monohydrate, but because their acquisition cost is dramatically lower (less than one-tenth of the 4-week cost), the overall total cost is significantly lower.

The probabilistic analysis indicates that there is a great deal of uncertainty as to which sequence is optimal (i.e. most cost-effective). No single sequence was most cost-effective at a £20,000 per QALY willingness to pay threshold in more than 40% of simulations; however, looking across strategies indicates that those starting with once daily potent corticosteroid were optimal in 84% of simulations. In 49% of all simulations, following once daily potent with twice daily very potent was optimal. In the remaining 16% of simulations, a sequence starting with either once or twice daily very potent corticosteroid was likely to be most cost-effective. This trend can also be seen by looking

at the rank order of strategies in Table 13, wherein those starting with potent corticosteroids have the highest mean net benefits, followed by those starting with very potent corticosteroids. These statistics indicate that we can be reasonably confident that starting with once daily potent corticosteroid is going to bring the greatest benefit for resources used, and that moving to a very potent corticosteroid, either once or twice daily is likely to provide further benefit at reasonable extra cost.

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 OD - VPS OD - VPS BD	128	33	to	270	0.774	0.758	to	0.79	15360
PS OD - VPS BD - TCF OD	142	37	to	304	0.775	0.759	to	0.791	15354
PS OD - PS BD - VPS BD	132	36	to	258	0.774	0.758	to	0.79	15352
PS OD - VPS BD - Vit D OD	146	35	to	300	0.774	0.758	to	0.79	15343
PS OD - VPS BD - Vit D BD	153	40	to	301	0.774	0.758	to	0.79	15334
PS OD - VPS BD - Coal tar polytherapy	155	41	to	297	0.774	0.758	to	0.79	15329
PS OD - Vit D OD - VPS BD	173	42	to	332	0.774	0.758	to	0.79	15308
VPS OD - VPS BD - TCF OD	177	70	to	329	0.774	0.758	to	0.79	15303
PS OD - Vit D BD - VPS BD	181	49	to	329	0.774	0.757	to	0.79	15298
PS OD - VPS BD - Referral	191	53	to	352	0.774	0.758	to	0.79	15289
VPS OD - VPS BD - Vit D OD	183	68	to	330	0.774	0.757	to	0.79	15288
PS BD - VPS OD - VPS BD	171	75	to	292	0.773	0.757	to	0.789	15285
PS OD - PS BD - VPS OD	188	36	to	427	0.774	0.756	to	0.79	15283
VPS BD - Vit D OD - TCF OD	214	94	to	383	0.775	0.759	to	0.79	15281
PS OD - TCF OD - VPS BD	213	57	to	390	0.775	0.759	to	0.791	15281
PS BD - VPS BD - TCF OD	187	90	to	317	0.773	0.758	to	0.79	15281
VPS OD - VPS BD - Vit D BD	195	74	to	339	0.773	0.757	to	0.79	15272
PS OD - VPS OD - TCF OD	211	35	to	547	0.774	0.757	to	0.79	15270
VPS OD - VPS BD - Coal tar polytherapy	198	75	to	333	0.773	0.757	to	0.79	15266
VPS BD - VIt D BD - TCF OD	228	113	to	383	0.775	0.759	to	0.79	15265
PS BD - VPS BD - Vit D OD	193	86	to	321	0.773	0.757	to	0.789	15264
VPS BD - TCF OD - Vit D BD	238	122	to	391	0.775	0.759	to	0.79	15261
Vit D OD - PS OD - VPS BD	199	118	to	328	0.773	0.756	to	0.789	15261
VPS BD - TCF OD - Coal tar polytherapy	239	121	to	386	0.775	0.759	to	0.79	15258
PS OD - PS BD - TCF OD	223	42	to	532	0.774	0.757	to	0.79	15255
PS OD - VPS OD - Vit D OD	218	33	to	532	0.773	0.756	to	0.79	15250
VPS BD - Vit D OD - VIt D BD	233	102	to	382	0.774	0.758	to	0.79	15248
VPS OD - Vit D OD - VPS BD	215	83	to	360	0.773	0.756	to	0.79	15247
Vit D BD - PS OD - VPS BD	204	116	to	329	0.772	0.756	to	0.789	15246
PS BD - VPS BD - Vit D BD	208	101	to	334	0.773	0.756	to	0.789	15245
VPS BD - Vit D OD - Coal tar polytherapy	236	104	to	381	0.774	0.758	to	0.79	15242
PS BD - VPS BD - Coal tar	211	104	to	332	0.772	0.756	to	0.789	15238

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @ £20k
polytherapy									
PS OD - VPS OD - VIt D BD	230	38	to	531	0.773	0.756	to	0.79	15236
PS OD - Vit D OD - VPS OD	233	42	to	539	0.773	0.756	to	0.79	15233
PS OD - PS BD - Vit D OD	231	40	to	512	0.773	0.756	to	0.79	15232
PS OD - VPS OD - Coal tar polytherapy	232	40	to	508	0.773	0.755	to	0.79	15229
VPS OD - Vit D BD - VPS BD	228	92	to	369	0.773	0.756	to	0.789	15229
PS OD - TCF OD - VPS OD	255	57	to	568	0.774	0.758	to	0.79	15229
Vit D OD - VPS OD - VPS BD	227	130	to	355	0.773	0.756	to	0.789	15226
PS OD - TCF OD - PS BD	262	58	to	562	0.774	0.757	to	0.79	15220
VPS BD - TCF OD - Referral	274	136	to	438	0.775	0.759	to	0.79	15220
PS BD - Vit D OD - VPS BD	229	116	to	350	0.772	0.756	to	0.789	15219
PS OD - Vit D OD - PS BD	245	46	to	519	0.773	0.755	to	0.79	15218
VPS OD - VPS BD - Referral	241	101	to	387	0.773	0.756	to	0.789	15217
PS OD - Vit D BD - VPS OD	246	47	to	535	0.773	0.756	to	0.79	15217
PS OD - PS BD - Vit D BD	245	48	to	509	0.773	0.755	to	0.789	15216
VPS BD - Vit D BD - Coal tar polytherapy	256	126	to	394	0.774	0.757	to	0.79	15215
VPS OD - TCF OD - VPS BD	263	113	to	414	0.774	0.758	to	0.79	15215
Vit D OD - PS BD - VPS BD	234	140	to	347	0.772	0.755	to	0.789	15214
PS OD - PS BD - Coal Tar polytherapy	247	51	to	493	0.773	0.755	to	0.789	15208
Vit D BD - VPS OD - VPS BD	239	140	to	365	0.772	0.755	to	0.789	15201
PS OD - Vit D OD - TCF OD	272	44	to	653	0.774	0.756	to	0.79	15200
PS OD - Vit D BD - PS BD	258	56	to	519	0.773	0.755	to	0.789	15200
PS BD - Vit D BD - VPS BD	244	133	to	365	0.772	0.756	to	0.789	15199
Vit D BD - VPS BD - TCF OD	258	157	to	399	0.773	0.756	to	0.789	15196
TCF OD - VPS OD - VPS BD	305	234	to	401	0.775	0.759	to	0.79	15189
VPS BD - Vit D OD - Referral	284	127	to	439	0.774	0.757	to	0.79	15188
Vit D BD - PS BD - VPS BD	248	157	to	359	0.772	0.755	to	0.789	15186
Vit D OD - PS OD - VPS OD	259	118	to	536	0.772	0.754	to	0.789	15186
PS OD - Vit D BD - TCF OD	285	54	to	640	0.774	0.756	to	0.79	15185
PS BD - TCF OD - VPS BD	283	163	to	404	0.773	0.757	to	0.79	15183
PS BD - VPS BD - Referral	261	139	to	389	0.772	0.755	to	0.789	15183
TCF OD - PS BD - VPS BD	309	238	to	392	0.775	0.759	to	0.79	15182
PS OD - TCF OD - Vit D BD	295	59	to	648	0.774	0.757	to	0.79	15181
PS OD - TCF OD - Coal Tar polytherapy	296	61	to	640	0.774	0.756	to	0.79	15177
PS BD - VPS OD - TCF OD	275	89	to	543	0.772	0.756	to	0.789	15175
PS OD - VPS OD - Referral	282	50	to	566	0.773	0.755	to	0.789	15175
Vit D OD - PS OD - PS BD	270	121	to	514	0.772	0.754	to	0.789	15171
TCF OD - VPS BD - Vit D BD	328	254	to	435	0.775	0.759	to	0.79	15165
Vit D BD - PS OD - VPS OD	269	118	to	531	0.772	0.754	to	0.789	15165

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @ £20k
PS OD - Vit D OD - VIt D BD	293	49	to	621	0.773	0.755	to	0.79	15162
TCF OD - VPS BD - Coal tar polytherapy	329	252	to	431	0.775	0.759	to	0.79	15162
VPS BD - Vit D BD - Referral	309	165	to	458	0.773	0.757	to	0.789	15156
PS OD - Vit D OD - Coal tar polytherapy	295	50	to	608	0.772	0.754	to	0.789	15155
Vit D OD - PS OD - TCF OD	298	121	to	645	0.773	0.755	to	0.79	15154
Vit D OD - VPS BD - TCF OD	298	143	to	545	0.773	0.756	to	0.789	15153
Vit D BD - PS OD - PS BD	281	125	to	511	0.771	0.754	to	0.789	15148
PS OD - PS BD - Referral	302	72	to	547	0.772	0.755	to	0.789	15147
Vit D BD - VPS BD - Coal tar polytherapy	286	175	to	406	0.772	0.754	to	0.789	15147
PS BD - VPS OD - Vit D OD	286	84	to	531	0.772	0.754	to	0.789	15146
Vit D OD - Vit D BD - VPS BD	299	164	to	427	0.772	0.755	to	0.789	15140
Vit D BD - PS OD - TCF OD	308	124	to	634	0.772	0.755	to	0.789	15133
PS OD - TCF OD - Referral	338	66	to	697	0.773	0.756	to	0.79	15131
TCF OD - Vit D BD - VPS BD	354	266	to	464	0.774	0.758	to	0.79	15131
PS OD - Vit D BD - Coal Tar polytherapy	314	66	to	602	0.772	0.754	to	0.789	15131
VPS OD - Vit D OD - TCF OD	326	96	to	659	0.773	0.755	to	0.79	15128
TCF OD - VPS BD - Referral	364	271	to	481	0.774	0.758	to	0.79	15124
PS BD - Vit D OD - VPS OD	306	117	to	537	0.771	0.754	to	0.789	15123
Vit D OD - TCF OD - VPS BD	340	186	to	480	0.773	0.757	to	0.79	15123
PS BD - TCF OD - VPS OD	336	170	to	566	0.773	0.756	to	0.789	15118
Vit D OD - PS BD - VPS OD	311	139	to	531	0.771	0.753	to	0.789	15118
TCF OD - PS BD - VPS OD	361	256	to	553	0.774	0.757	to	0.79	15117
PS BD - VPS OD - Vit D BD	309	96	to	547	0.771	0.753	to	0.789	15117
Vit D OD - PS OD - Vit D BD	318	124	to	614	0.772	0.753	to	0.789	15115
Vit D OD - VPS BD - Vit D BD	323	150	to	534	0.772	0.754	to	0.789	15109
Vit D OD - PS OD - Coal tar polytherapy	321	126	to	601	0.771	0.753	to	0.789	15108
Vit D OD - VPS OD - TCF OD	338	139	to	651	0.772	0.754	to	0.789	15107
PS BD - VPS OD - Coal Tar polytherapy	313	97	to	534	0.771	0.753	to	0.789	15107
VPS OD - Vit D BD - TCF OD	348	111	to	656	0.772	0.755	to	0.789	15102
Vit D OD - VPS BD - Coal tar polytherapy	326	152	to	528	0.771	0.753	to	0.789	15100
VPS OD - TCF OD - Vit D BD	359	125	to	663	0.773	0.755	to	0.789	15099
PS OD - VIt D OD - Referral	350	59	to	656	0.772	0.754	to	0.789	15094
VPS OD - TCF OD - Coal tar polytherapy	360	127	to	646	0.773	0.755	to	0.79	15093
PS BD - Vit D BD - VPS OD	330	131	to	551	0.771	0.753	to	0.789	15091
Vit D BD - TCF OD - VPS BD	363	252	to	481	0.773	0.756	to	0.789	15090
PS BD - Vit D OD - TCF OD	351	134	to	632	0.772	0.755	to	0.789	15088

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @ £20k
Vit D BD - VPS BD - Referral	339	217	to	469	0.771	0.754	to	0.789	15087
Vit D OD - PS BD - TCF OD	356	154	to	626	0.772	0.754	to	0.789	15083
Vit D BD - PS BD - VPS OD	334	155	to	545	0.771	0.752	to	0.788	15079
Vit D BD - PS OD - Coal Tar polytherapy	336	133	to	596	0.771	0.752	to	0.788	15079
Vit D OD - Vit D BD - PS OD	347	150	to	623	0.771	0.752	to	0.789	15079
VPS OD - Vit D OD - Vit D BD	357	99	to	638	0.772	0.753	to	0.789	15074
Vit D BD - VPS OD - TCF OD	359	157	to	651	0.772	0.754	to	0.789	15074
TCF OD - VPS OD - Vit D BD	400	264	to	648	0.774	0.756	to	0.79	15073
TCF OD - VPS OD - Coal tar polytherapy	402	263	to	632	0.773	0.756	to	0.79	15068
PS OD - Vit D BD - Referral	371	86	to	647	0.772	0.753	to	0.789	15066
VPS OD - Vit D OD - Coal Tar polytherapy	360	101	to	626	0.771	0.752	to	0.789	15064
PS BD - Vit D BD - TCF OD	376	168	to	639	0.772	0.754	to	0.789	15059
PS BD - TCF OD - Vit D BD	389	190	to	644	0.772	0.755	to	0.789	15055
TCF - Vit D BD - VPS OD	415	275	to	654	0.774	0.756	to	0.79	15055
TCF OD - PS BD - Vit D BD	414	273	to	629	0.773	0.756	to	0.79	15054
Vit D OD - VPS OD - Vit D BD	369	145	to	632	0.771	0.752	to	0.789	15053
Vit D OD - TCF OD - VPS OD	396	187	to	672	0.772	0.755	to	0.789	15053
PS BD - TCF OD - Coal Tar polytherapy	391	196	to	631	0.772	0.755	to	0.789	15049
TCF OD - PS BD - Coal Tar polytherapy	416	273	to	615	0.773	0.755	to	0.79	15048
Vit D OD - PS OD - Referral	375	135	to	650	0.771	0.752	to	0.788	15047
Vit D BD - PS BD - TCF OD	380	192	to	633	0.771	0.754	to	0.789	15047
Vit D OD - VPS OD - Coal tar polytherapy	372	147	to	620	0.771	0.752	to	0.789	15044
VPS OD - TCF OD - Referral	407	142	to	703	0.772	0.754	to	0.789	15041
TCF OD - Vit D BD - PS BD	427	281	to	638	0.773	0.756	to	0.79	15039
Vit D OD - TCF OD - PS BD	406	190	to	655	0.772	0.755	to	0.789	15039
Vit D OD - VPS BD - Referral	384	184	to	578	0.771	0.752	to	0.789	15037
PS BD - VPS OD - Referral	377	141	to	583	0.771	0.752	to	0.788	15034
Vit D OD - Vit D BD - VPS OD	388	168	to	638	0.771	0.752	to	0.789	15029
PS BD - Vit D OD - Vit D BD	387	146	to	625	0.771	0.752	to	0.788	15027
VPS OD - Vit D BD - Coal Tar polytherapy	391	116	to	637	0.771	0.752	to	0.789	15024
Vit D OD - PS BD - Vit D BD	392	168	to	618	0.771	0.752	to	0.788	15022
TCF OD - VPS OD - Referral	449	278	to	686	0.773	0.755	to	0.79	15015
PS BD - Vit D OD - Coal Tar polytherapy	391	149	to	610	0.77	0.751	to	0.788	15015
Vit D BD - PS OD - Referral	394	156	to	640	0.77	0.751	to	0.788	15014
VIt D BD - TCF OD - VPS OD	424	254	to	672	0.772	0.754	to	0.789	15014
Vit D OD - PS BD - Coal tar	396	171	to	603	0.77	0.751	to	0.788	15010

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @ £20k
polytherapy									
Vit D OD - Vit D BD - PS BD	408	182	to	625	0.771	0.752	to	0.789	15003
Vit D BD - TCF OD - PS BD	435	263	to	656	0.772	0.754	to	0.789	14998
Vit D BD - VPS OD - Coal tar polytherapy	403	169	to	630	0.77	0.751	to	0.788	14996
VPS OD - Vit D OD - Referral	422	131	to	669	0.771	0.752	to	0.789	14995
PS BD - TCF OD - Referral	443	220	to	682	0.772	0.754	to	0.789	14990
Vit D OD - Vit D BD - TCF OD	440	181	to	740	0.771	0.753	to	0.789	14990
TCF OD - PS BD - Referral	469	299	to	666	0.773	0.755	to	0.789	14989
Vit D OD - TCF OD - Vit D BD	452	194	to	747	0.772	0.754	to	0.789	14987
Vit D OD - TCF OD - Coal Tar polytherapy	454	195	to	736	0.772	0.753	to	0.789	14980
TCF OD - Vit D BD - Coal Tar polytherapy	479	290	to	711	0.773	0.754	to	0.789	14975
Vit D OD - VPS OD - Referral	434	175	to	663	0.77	0.751	to	0.788	14974
PS BD - Vit D BD - Coal Tar polytherapy	427	186	to	619	0.77	0.751	to	0.788	14969
Vit D BD - PS BD - Coal Tar polytherapy	431	214	to	612	0.769	0.75	to	0.788	14956
VPS OD - Vit D BD - Referral	458	167	to	677	0.77	0.751	to	0.789	14948
PS BD - Vit D OD - REferral	460	196	to	658	0.77	0.75	to	0.788	14937
Vit D BD - TCF OD - Coal Tar polytherapy	487	271	to	727	0.771	0.753	to	0.789	14934
Vit D OD - PS BD - Referral	465	215	to	651	0.77	0.75	to	0.788	14932
Vit D OD - TCF OD - Referral	506	205	to	788	0.771	0.752	to	0.789	14922
Vit D BD - VPS OD - Referral	470	217	to	670	0.769	0.75	to	0.788	14920
TCF OD - Vit D BD - Referral	534	320	to	761	0.772	0.754	to	0.789	14913
Vit D OD - Vit D BD - Coal Tar polytherapy	485	203	to	703	0.77	0.749	to	0.788	14906
PS BD - Vit D BD - referral	502	272	to	662	0.769	0.75	to	0.788	14884
Vit D BD - TCF OD - Referral	542	305	to	780	0.771	0.752	to	0.789	14872
Vit D BD - PS BD - Referral	506	297	to	655	0.769	0.749	to	0.788	14871
Vit D OD - Vit D BD - Referral	556	249	to	738	0.769	0.748	to	0.788	14825
Capasal only	548	231	to	696	0.767	0.746	to	0.787	14790
Vehicle only	611	572	to	649	0.765	0.744	to	0.787	14698

(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	Day Centre Care	Total (a)
PS OD - VPS OD - VPS BD	£38	£41	£24	£41	£143
PS OD - VPS BD - TCF OD	£73	£33	£14	£25	£145

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
PS OD - PS BD - VPS BD	£36	£41	£23	£40	£139
PS OD - VPS BD - Vit D OD	£51	£36	£24	£42	£153
PS OD - VPS BD - Vit D BD	£52	£37	£27	£47	£163
PS OD - VPS BD - Coal tar polytherapy	£42	£38	£31	£53	£165
PS OD - Vit D OD - VPS BD	£74	£42	£24	£42	£182
VPS OD - VPS BD - TCF OD	£98	£36	£22	£37	£192
PS OD - Vit D BD - VPS BD	£74	£44	£27	£47	£192
PS OD - VPS BD - Referral	£52	£36	£45	£75	£207
VPS OD - VPS BD - Vit D OD	£67	£41	£36	£60	£204
PS BD - VPS OD - VPS BD	£47	£54	£34	£58	£193
PS OD - PS BD - VPS OD	£45	£46	£39	£66	£195
VPS BD - Vit D OD - TCF OD	£130	£33	£22	£38	£223
PS OD - TCF OD - VPS BD	£147	£33	£14	£25	£220
PS BD - VPS BD - TCF OD	£96	£43	£21	£36	£196
VPS OD - VPS BD - Vit D BD	£69	£42	£40	£67	£218
PS OD - VPS OD - TCF OD	£104	£41	£24	£42	£211
VPS OD - VPS BD - Coal tar polytherapy	£55	£44	£45	£76	£220
VPS BD - VIt D BD - TCF OD	£136	£35	£25	£42	£238
PS BD - VPS BD - Vit D OD	£65	£48	£35	£60	£208
VPS BD - TCF OD - Vit D BD	£151	£29	£25	£42	£247
Vit D OD - PS OD - VPS BD	£90	£47	£24	£42	£204
VPS BD - TCF OD - Coal tar polytherapy	£141	£31	£28	£48	£248
PS OD - PS BD - TCF OD	£102	£41	£24	£41	£207
PS OD - VPS OD - Vit D OD	£69	£46	£41	£69	£225
VPS BD - Vit D OD - VIt D BD	£100	£39	£41	£70	£251
VPS OD - Vit D OD - VPS BD	£95	£48	£36	£60	£240
Vit D BD - PS OD - VPS BD	£87	£51	£27	£47	£212
PS BD - VPS BD - Vit D BD	£67	£49	£39	£67	£222
VPS BD - Vit D OD - Coal tar polytherapy	£85	£41	£47	£80	£253
PS BD - VPS BD - Coal tar polytherapy	£53	£51	£45	£76	£225
PS OD - VPS OD - VIt D BD	£72	£48	£45	£77	£242
PS OD - Vit D OD - VPS OD	£84	£47	£41	£69	£241
PS OD - PS BD - Vit D OD	£66	£46	£41	£69	£222
PS OD - VPS OD - Coal tar polytherapy	£55	£50	£52	£88	£244
VPS OD - Vit D BD - VPS BD	£96	£51	£40	£67	£253
PS OD - TCF OD - VPS OD	£152	£37	£24	£42	£255
Vit D OD - VPS OD - VPS BD	£101	£55	£36	£60	£253
PS OD - TCF OD - PS BD	£151	£36	£24	£41	£252

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
VPS BD - TCF OD - Referral	£150	£28	£41	£68	£288
PS BD - Vit D OD - VPS BD	£95	£55	£35	£60	£245
PS OD - Vit D OD - PS BD	£81	£47	£41	£69	£238
VPS OD - VPS BD - Referral	£69	£41	£61	£100	£271
PS OD - Vit D BD - VPS OD	£85	£50	£45	£77	£257
PS OD - PS BD - Vit D BD	£69	£48	£45	£77	£239
VPS BD - Vit D BD - Coal tar polytherapy	£87	£44	£52	£88	£272
VPS OD - TCF OD - VPS BD	£190	£37	£22	£37	£286
Vit D OD - PS BD - VPS BD	£98	£56	£35	£60	£249
PS OD - PS BD - Coal Tar polytherapy	£52	£50	£52	£88	£243
Vit D BD - VPS OD - VPS BD	£99	£59	£40	£67	£265
PS OD - Vit D OD - TCF OD	£143	£42	£25	£43	£253
PS OD - Vit D BD - PS BD	£82	£50	£45	£77	£255
PS BD - Vit D BD - VPS BD	£95	£58	£39	£67	£259
Vit D BD - VPS BD - TCF OD	£155	£47	£25	£42	£270
TCF OD - VPS OD - VPS BD	£225	£38	£22	£37	£320
VPS BD - Vit D OD - Referral	£100	£38	£64	£106	£308
Vit D BD - PS BD - VPS BD	£96	£60	£39	£67	£262
Vit D OD - PS OD - VPS OD	£99	£52	£41	£69	£262
PS OD - Vit D BD - TCF OD	£151	£44	£28	£48	£272
PS BD - TCF OD - VPS BD	£193	£44	£21	£36	£294
PS BD - VPS BD - Referral	£67	£48	£62	£102	£279
TCF OD - PS BD - VPS BD	£222	£38	£21	£36	£317
PS OD - TCF OD - Vit D BD	£168	£38	£28	£48	£282
PS OD - TCF OD - Coal Tar polytherapy	£157	£39	£33	£55	£284
PS BD - VPS OD - TCF OD	£140	£54	£35	£60	£288
PS OD - VPS OD - Referral	£71	£46	£71	£117	£305
Vit D OD - PS OD - PS BD	£97	£53	£41	£69	£259
TCF OD - VPS BD - Vit D BD	£237	£34	£25	£42	£339
Vit D BD - PS OD - VPS OD	£98	£56	£45	£77	£276
PS OD - Vit D OD - VIt D BD	£109	£50	£48	£81	£287
TCF OD - VPS BD - Coal tar polytherapy	£228	£35	£28	£48	£340
VPS BD - Vit D BD - Referral	£104	£40	£70	£116	£330
PS OD - Vit D OD - Coal tar polytherapy	£91	£52	£55	£93	£291
Vit D OD - PS OD - TCF OD	£159	£48	£25	£43	£275
Vit D OD - VPS BD - TCF OD	£198	£55	£37	£63	£353
Vit D BD - PS OD - PS BD	£95	£57	£45	£77	£274
PS OD - PS BD - Referral	£68	£44	£72	£120	£304
Vit D BD - VPS BD - Coal tar	£106	£57	£52	£88	£303

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
polytherapy					
PS BD - VPS OD - Vit D OD	£91	£61	£58	£99	£310
Vit D OD - Vit D BD - VPS BD	£151	£60	£41	£70	£322
Vit D BD - PS OD - TCF OD	£164	£51	£28	£48	£291
PS OD - TCF OD - Referral	£167	£35	£47	£79	£329
TCF OD - Vit D BD - VPS BD	£258	£40	£25	£42	£365
PS OD - Vit D BD - Coal Tar polytherapy	£94	£55	£61	£103	£314
VPS OD - Vit D OD - TCF OD	£192	£48	£37	£63	£340
TCF OD - VPS BD - Referral	£237	£33	£41	£68	£379
PS BD - Vit D OD - VPS OD	£109	£62	£58	£99	£328
Vit D OD - TCF OD - VPS BD	£252	£45	£22	£38	£357
PS BD - TCF OD - VPS OD	£201	£48	£35	£60	£344
Vit D OD - PS BD - VPS OD	£112	£63	£58	£99	£332
TCF OD - PS BD - VPS OD	£231	£42	£35	£60	£367
PS BD - VPS OD - Vit D BD	£95	£63	£64	£110	£332
Vit D OD - PS OD - Vit D BD	£125	£55	£48	£81	£309
Vit D OD - VPS BD - Vit D BD	£151	£66	£68	£115	£399
Vit D OD - PS OD - Coal tar polytherapy	£107	£58	£55	£93	£312
Vit D OD - VPS OD - TCF OD	£198	£55	£37	£63	£353
PS BD - VPS OD - Coal Tar polytherapy	£72	£66	£73	£124	£336
VPS OD - Vit D BD - TCF OD	£202	£51	£41	£70	£364
Vit D OD - VPS BD - Coal tar polytherapy	£128	£69	£77	£129	£402
VPS OD - TCF OD - Vit D BD	£221	£43	£41	£70	£375
PS OD - VIt D OD - Referral	£109	£45	£75	£125	£354
VPS OD - TCF OD - Coal tar polytherapy	£206	£45	£47	£80	£378
PS BD - Vit D BD - VPS OD	£111	£66	£64	£110	£351
Vit D BD - TCF OD - VPS BD	£261	£49	£25	£42	£377
PS BD - Vit D OD - TCF OD	£193	£56	£37	£62	£347
Vit D BD - VPS BD - Referral	£122	£53	£70	£116	£361
Vit D OD - PS BD - TCF OD	£195	£56	£37	£62	£351
Vit D BD - PS BD - VPS OD	£112	£68	£64	£110	£354
Vit D BD - PS OD - Coal Tar polytherapy	£106	£62	£61	£103	£333
Vit D OD - Vit D BD - PS OD	£150	£62	£48	£81	£341
VPS OD - Vit D OD - Vit D BD	£145	£58	£68	£115	£386
Vit D BD - VPS OD - TCF OD	£206	£59	£41	£70	£376
TCF OD - VPS OD - Vit D BD	£255	£44	£41	£70	£410
TCF OD - VPS OD - Coal tar polytherapy	£240	£46	£47	£80	£412

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
PS OD - Vit D BD - Referral	£113	£48	£82	£137	£380
VPS OD - Vit D OD - Coal Tar polytherapy	£122	£61	£77	£129	£389
PS BD - Vit D BD - TCF OD	£203	£59	£41	£70	£372
PS BD - TCF OD - Vit D BD	£223	£51	£41	£70	£384
TCF - Vit D BD - VPS OD	£268	£46	£41	£70	£424
TCF OD - PS BD - Vit D BD	£252	£44	£41	£70	£407
Vit D OD - VPS OD - Vit D BD	£151	£66	£68	£115	£399
Vit D OD - TCF OD - VPS OD	£260	£50	£37	£63	£410
PS BD - TCF OD - Coal Tar polytherapy	£207	£53	£47	£80	£387
TCF OD - PS BD - Coal Tar polytherapy	£237	£46	£47	£80	£410
Vit D OD - PS OD - Referral	£124	£51	£75	£125	£375
Vit D BD - PS BD - TCF OD	£203	£60	£41	£70	£374
Vit D OD - VPS OD - Coal tar polytherapy	£128	£69	£77	£129	£402
VPS OD - TCF OD - Referral	£221	£42	£65	£107	£435
TCF OD - Vit D BD - PS BD	£265	£46	£41	£70	£422
Vit D OD - TCF OD - PS BD	£258	£50	£37	£62	£407
Vit D OD - VPS BD - Referral	£151	£64	£100	£164	£480
PS BD - VPS OD - Referral	£95	£62	£96	£158	£411
Vit D OD - Vit D BD - VPS OD	£167	£69	£68	£115	£418
PS BD - Vit D OD - Vit D BD	£144	£67	£69	£116	£396
VPS OD - Vit D BD - Coal Tar polytherapy	£125	£66	£85	£142	£418
Vit D OD - PS BD - Vit D BD	£147	£67	£69	£116	£400
TCF OD - VPS OD - Referral	£255	£42	£65	£107	£469
PS BD - Vit D OD - Coal Tar polytherapy	£120	£70	£79	£132	£402
Vit D BD - PS OD - Referral	£125	£54	£82	£137	£399
VIt D BD - TCF OD - VPS OD	£271	£54	£41	£70	£436
Vit D OD - PS BD - Coal tar polytherapy	£123	£71	£79	£132	£405
Vit D OD - Vit D BD - PS BD	£163	£69	£69	£116	£418
Vit D BD - TCF OD - PS BD	£268	£54	£41	£70	£433
Vit D BD - VPS OD - Coal tar polytherapy	£129	£74	£85	£142	£430
VPS OD - Vit D OD - Referral	£145	£57	£100	£164	£466
PS BD - TCF OD - Referral	£223	£47	£66	£110	£445
Vit D OD - Vit D BD - TCF OD	£263	£61	£43	£73	£440
TCF OD - PS BD - Referral	£252	£40	£66	£110	£468
Vit D OD - TCF OD - Vit D BD	£283	£52	£43	£73	£452
Vit D OD - TCF OD - Coal Tar polytherapy	£267	£55	£50	£84	£455

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
TCF OD - Vit D BD - Coal Tar polytherapy	£275	£51	£56	£94	£475
Vit D OD - VPS OD - Referral	£151	£64	£100	£164	£480
PS BD - Vit D BD - Coal Tar polytherapy	£124	£75	£88	£147	£433
Vit D BD - PS BD - Coal Tar polytherapy	£125	£76	£88	£147	£435
VPS OD - Vit D BD - Referral	£151	£61	£109	£177	£498
PS BD - Vit D OD - REferral	£145	£60	£103	£170	£478
Vit D BD - TCF OD - Coal Tar polytherapy	£279	£59	£56	£94	£487
Vit D OD - PS BD - Referral	£147	£61	£103	£170	£482
Vit D OD - TCF OD - Referral	£283	£48	£69	£114	£514
Vit D BD - VPS OD - Referral	£155	£69	£109	£177	£510
TCF OD - Vit D BD - Referral	£293	£44	£75	£125	£537
Vit D OD - Vit D BD - Coal Tar polytherapy	£181	£78	£92	£153	£504
PS BD - Vit D BD - referral	£150	£64	£113	£185	£512
Vit D BD - TCF OD - Referral	£296	£52	£75	£125	£548
Vit D BD - PS BD - Referral	£151	£66	£113	£185	£514
Vit D OD - Vit D BD - Referral	£208	£66	£117	£192	£583
Capasal only	£116	£99	£130	£211	£557
Vehicle only	£112	£109	£149	£238	£609
Vehicle only	£112	£109	£149	£238	£609

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

N.3.2 Sensitivity analyses

A series of scenario analysis suggested that the conclusions from the base case are somewhat sensitive to changes in assumptions made.

N.3.2.1 Lower expected resource use for combined product containing betamethasone dipropionate and calcipotriol monohydrate

The base case of this analysis assumed that patient using combined product containing betamethasone dipropionate and calcipotriol monohydrate for 4 weeks would use approximate 71.4 g of product. This estimate was based on the mean across five RCTs[3-7]. In a recent UK cost-utility analysis, Affleck and colleagues[1] assumed the 4-week quantity used to be 60 g. At this quantity, the unit cost of combined product containing betamethasone dipropionate and calcipotriol monohydrate is cut nearly in half. This value was used in a sensitivity analysis to explore how sensitivity the results were to this particular value.

The results suggest that the conclusions are insensitive to variation in this parameter. Here, as in the base case, the most cost-effective strategy is once daily potent corticosteroid followed by twice daily very potent corticosteroid and then once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate. The ICER comes down to £12,093 in this sensitivity analysis compared to £14,430 in the base case. Even at this reduced cost though, combined product

containing betamethasone dipropionate and calcipotriol monohydrate does not represent better value for NHS resources than potent or very potent corticosteroids alone as a first-line strategy.

N.3.2.2 Restricted comparators

The base case analysis put a few conditions on the way topicals could be sequenced (see Table 1 in section N.2.1.1. These did not restrict how potent and very potent corticosteroids were fit into treatment sequences. The GDG expressed concern that this lack of restrictions may not fully reflect the way these topicals are and should be used in general practice. They indicated that much more caution is and should be used when prescribing potent and very potent corticosteroids for both continuous and intermittent use. The GDG was also concerned that the analysis did not fully capture the safety risks associated with the use of these agents. In a stepwise fashion, various additional restrictions were placed on the use of these agents in each sequence.

In the first scenario, all strategies involving potent or very potent corticosteroids (including two compound formulation product) in all three lines of treatment were removed. The results confirmed the findings of the base case results in which once daily potent corticosteroid then twice daily very potent corticosteroid was found to be most cost-effective as first and second-line treatments. However, in this scenario no further steroid could be prescribed; therefore once daily vitamin D or vitamin D analogue was found to be the most cost-effective third line treatment.

In the second scenario, no sequence could include the consecutive use of potent or very potent corticosteroid, including as part of combined product containing betamethasone dipropionate and calcipotriol monohydrate. The results again showed the likely cost-effectiveness of strategies including potent and very potent corticosteroids. Here, starting with once daily potent corticosteroids and then moving to once daily vitamin D or vitamin D analogue and then twice daily very potent corticosteroids was least costly and second most effective. Starting the sequence with twice daily very potent corticosteroid and ending with once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate generated 0.00118 more QALYs, but at an additional cost of £45.90 per year. The resulting ICER (£38,898) is thus over the £20,000 per QALY threshold.

In the third scenario, twice daily application of very potent corticosteroid could not precede once daily application. Under this condition, a strategy of starting with once daily potent corticosteroid and then escalating up to once daily very potent corticosteroid and then finally up to twice daily very potent corticosteroid was most likely to be cost-effective. Starting with once and then twice daily very potent corticosteroid and ending with once daily TCF produce produced an additional 0.00012 QALYs, but at an additional cost of £52.60 (ICER=£438,333).

If these conditions are combined with those outlined in scenarios 1 and 2, then the optimal sequence is to start with once daily very potent corticosteroid then move to once daily vitamin D or vitamin D analogue and finally to twice daily very potent corticosteroid. A strategy of starting with once daily potent corticosteroids, followed by once daily vitamin D or vitamin D analogue and then ended with once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate generates an additional 0.00002 QALYs, but at a cost of £31.10 (ICER=£1.56 million) making it unlikely to be cost-effective by the NICE willingness to pay threshold.

In addition to the concerns raised about the safety of potent and very potent corticosteroids, the GDG raised the issue of cosmetic acceptability and its importance in the treatment of scalp psoriasis. In particular, they voiced a strong preference for once daily application, stating that few patients would be willing or interested in applying topicals to their scalp more than once a day, specifically at night. On that basis, modelled comparators were restricted in a stepwise fashion.

In the first scenario, twice daily strategies were reserved for third line treatment following failure of at least two once daily strategies. If steroids could be offered in all three lines of treatment, then the

optimal sequence was to start with once daily potent corticosteroid, move up to once daily very potent corticosteroid and then escalate to twice daily very potent corticosteroid if necessary. If one is looking to avoid using very potent corticosteroids first or second line in the sequence, then the next most cost-effective sequence under these conditions was once daily vitamin D as a second option following initial once daily potent corticosteroid, and still ending with twice daily very potent corticosteroid would still be the most cost-effective third line topical. Replacing vitamin D or vitamin D analogue with once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate in this sequence is expected to yield an additional 0.00066 QALYs for an extra £36.20 per year (ICER=£54,848).

In a second scenario, all twice daily strategies were removed and only sequences of once daily treatments were included. If steroids could be offered anywhere in the sequence, then the most cost-effective strategy was to start with potent corticosteroids, move up to very potent corticosteroids and then try combined product containing betamethasone dipropionate and calcipotriol monohydrate if both steroids alone have failed. Moving combined product containing betamethasone dipropionate and calcipotriol monohydrate from the end of the sequence to the beginning is expected to produce an additional 0.00013 QALYs at an additional cost of £112 per year (ICER=£862,308). If one wishes to avoid consecutive use of steroids, then the optimal strategy is to start with potent steroids, then switch to vitamin D or vitamin D analogues and end with very potent corticosteroids. Replacing very potent corticosteroids with combined product containing betamethasone dipropionate and calcipotriol monohydrate in this sequence generates 0.00032 more QALYs, but with an ICER too high to be considered cost-effective (ICER=£64,375).

N.4 Discussion

N.4.1 Summary of results

In assessing the relative cost-effectiveness of alternative topical therapies in patients with moderate to severe scalp psoriasis limited evidence was available from the published economic literature. The evidence that was identified and included in the health economic review had potentially serious limitations and therefore the GDG considered it a priority to undertake original evaluation for the guideline in order to inform recommendations.

Original decision modelling undertaken for the guideline showed that there were relatively small differences in terms of benefit between 169 different topical sequences, but the differences in terms of cost were quite substantial. Based on the mean costs and benefits, the analysis suggests that initial treatment with once daily potent corticosteroid followed by twice daily very potent corticosteroid and then once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate if steroids alone are insufficient to induce clearance or near clearance is likely to represent the most cost-effective sequence for moderate to severe scalp psoriasis. Uncertainties in the analysis were explored through sensitivity analysis which showed that in some scenarios in which restrictions were placed on the comparators

- Once daily vitamin D or vitamin D analogue might be cost-effective second or third in the sequence, after trials of potent or very potent corticosteroids
- Combined product containing betamethasone dipropionate and calcipotriol monohydrate is likely to be cost-effective third in sequences, after potent and very potent corticosteroids and when only once daily applications of topicals are being considered

In general, sequences ending with once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate were slightly more effective than the same sequence ending with alternatives such as vitamin D or vitamin D analogue or potent corticosteroid; however, the very modest additional benefit (<0.0007, dependent on comparator) would only be considered potentially cost-effective if willingness to pay thresholds were between £40,000 and £2 million per

QALY gained. If, however, the amount of combined product containing betamethasone dipropionate and calcipotriol monohydrate used by patients is less than reported in the clinical trial evidence, such that a single 60 g pack is needed for 4 weeks, then combined product containing betamethasone dipropionate and calcipotriol monohydrate may be more cost-effective earlier in a given sequence.

N.4.2 Limitations & interpretation

The analysis presented here 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 they can be assumed to have previously tried, succeeded and/or failed various topical treatments.

The analysis only captured the efficacy of topicals and did not capture the costs or consequences of adverse events. Although the RCT evidence on adverse events was sparse, the GDG is mindful of the risks associated with the long-term use of potent and very potent corticosteroids. They carefully considered whether the added effect in terms of clearance was worth the potential risks of adverse effects.

The model was also focused on the induction of disease clearance as opposed to the maintenance of clearance. No trials focusing on maintenance were identified in the clinical evidence review and therefore no evidence was available for use in the economic model.

The model also takes a relatively short time horizon considering that psoriasis of the scalp is a chronic, long term condition for which patients may take up treatment intermittently for many years of their lives. Frequency and severity of relapse, selection for and speed of onward referral, methods of self-management and long-term safety are all issues inadequately addressed in the evidence base and therefore translate into limitations of the economic analysis.

Considering both the strengths and weakness of the analysis, the GDG used it to inform their recommendations on the treatment of scalp psoriasis. The analysis showed that there were relatively small differences in terms of benefit between different topical sequences for scalp psoriasis, but large differences in terms of cost. Based on the mean costs and benefits of 169 compared sequences, the analysis found that initial treatment with once daily potent corticosteroids is likely to offer the best value for NHS resource.

The base case analysis showed that following a failure of potent corticosteroids, the optimal strategy is to try very potent corticosteroids. Treatment with twice daily was found to be more cost effective than once daily; however the GDG was concerned that very potent corticosteroids, although effective and cost-effective, are quite an aggressive strategy and carry greater risk of steroid-related adverse events, which were not captured in the economic model. The GDG thus looked to sensitivity analyses wherein very potent corticosteroids, once and twice daily, were reserved for third line treatment. Under such conditions, the optimal second-line therapy would be once daily vitamin D or vitamin D analogue or once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate (if mean quantity of topical used is under 60 g per month). If these topicals fail to bring about control of scalp psoriasis, then the optimal third-line treatment is twice daily very potent corticosteroids. 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. The GDG noted strong patient preference for once daily applications due to the messiness, inconvenience and

cosmetic acceptability of topicals applied to the scalp. Therefore, if escalation to twice daily very potent corticosteroids was considered unacceptable, then once daily very potent corticosteroid is likely offer the next best value for NHS resource.

The analysis also considered the cost-effectiveness of coal tar polytherapy (Capasal® shampoo) relative to other topicals in the treatment of scalp psoriasis. Coal tar based shampoo was only slightly more effective that placebo/vehicle scalp solution and far less effective than other topicals. In the model, this meant that more patients ended up failing treatment in primary care and being referred onward for specialist consultations and treatments, thus making the true costs to the NHS of treatment with coal tar shampoos much higher than the acquisition cost alone. The GDG was aware that coal tar based shampoos are regularly prescribed in primary care for treatment of scalp psoriasis and agreed that based on the evidence of clinical and cost-effectiveness that they are not optimal for the treatment of scalp psoriasis. In order to ensure more efficient use of NHS resources, they considered it important to discourage GPs from using this particular treatment modality.

N.4.3 Generalisability to other populations / settings

The results of this analysis may be most applicable to patients with localised psoriasis requiring only topical therapy for their scalp, but the results may also be applicable to patients for whom topical therapies may be offered in conjunction with other therapies, such as phototherapy or systemic therapy. Patients undergoing these more aggressive treatments are likely to have much more widespread and/or severe disease, but additional topical therapy for the scalp alone is likely to be beneficial.

This analysis of the treatment of psoriasis of the scalp is distinct from the analysis of the treatment of scalp of the trunk and/or limbs largely because it is based on a different evidence base and as such has given rise to site-specific recommendations. In clinical practice, health care professionals are likely to see patients who are dealing with psoriasis at a variety of sites, including their face and flexures. It is quite possible that health care professionals will need to prescribe different topicals for different sites, meaning that patients may have several different agents at a time. Indeed, even if they are using the same product (i.e. potent corticosteroid) on different sites, they may be prescribed different formulations for each site (i.e. creams or ointments for the trunk and limbs; gels or foams for the scalp). It would be simpler to prescribe one single treatment for all sites, but as the clinical and cost-effectiveness has shown, such an approach may not represent the most effective or efficient use of NHS resources.

N.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 Affleck and colleagues[1]. Affleck and colleagues found a sequence starting with twice daily potent corticosteroids followed by concurrent treatment (am/pm) with vitamin D or vitamin D analogue and potent corticosteroid and then once daily combined product containing betamethasone dipropionate and calcipotriol monohydrate to be most cost-effective. Although the analysis appears to have been executed well, the included comparators and the estimates of effect and resource use had limitations which called the conclusions of the analysis into question.

The biggest differences in the results of the NCGC analysis presented here and the analysis undertaken by Affleck has to do with the comparators included, namely the inclusion/exclusion of very potent corticosteroids. The NCGC analysis included very potent corticosteroids as the network meta-analysis demonstrated them to be highly efficacious in the short term treatment of psoriasis of the scalp. The GDG confirmed that although very potent corticosteroids are not normal management for the treatment of the trunks and limbs, they constitute a reasonable, short-term option for treating the scalp.

The second key difference between the analyses relates to the relative treatment effects used. Affleck and colleagues derived their treatment effects from an adjusted indirect comparison[13], which, when compared to the NCGC network meta-analysis, appears to have overestimated the effectiveness of combined product containing betamethasone dipropionate and calcipotriol monohydrate compared to other topicals. For example, in their analysis combined product containing betamethasone dipropionate and calcipotriol monohydrate was found to be 2.45 times more likely to induce response than once daily calcipotriol (RR=2.45, 95% CI: 1.84 to 3.27). The NCGC network meta-analysis found the risk ratio to be lower, around 1.614. This translates into an absolute risk difference between the two comparators of 35.54% using Affleck's estimates and 27.66% using the NCGC estimates. Differences such as these add up when synthesised in economic models and could lead to biased conclusions.

In addition, the estimate they used for quantity of combined product containing betamethasone dipropionate and calcipotriol monohydrate used per 4-week treatment period was 60 g, compared to the estimate used in the NCGC analysis 71.4 g. Based on these estimates of resource use, the NCGC analysis assumes 4 weeks of combined product containing betamethasone dipropionate and calcipotriol monohydrate costs £31.29 more than Affleck and colleagues did. We performed a sensitivity analysis in which we assumed the same quantity of combined product containing betamethasone dipropionate and calcipotriol monohydrate used by Affleck and colleagues (i.e. 60 g, £36.50). The ICER for combined product containing betamethasone dipropionate and calcipotriol monohydrate as a third line treatment improved compared to the base case (£19,286 vs £44,286), making it potentially cost-effective given the NICE willingness to pay threshold. However, there remains a great deal of uncertainty in this conclusion.

One thing that Affleck and colleagues were able to capture that the NCGC analysis was not had to do with the potential disutilities associated with adverse events. They included these in their base case, and unfortunately did not report a sensitivity analysis wherein they were removed altogether with which to compare. However, the authors did state that variation in the incidence of adverse events, upwards and downwards, did not change the conclusions of their analysis.

N.4.5 Conclusion

New economic analysis from a current UK NHS and PSS perspective comparing 169 different sequences of topical therapies found sequences beginning with once daily potent corticosteroids to offer the best value for NHS resource in the treatment of patients with moderate to severe scalp psoriasis. This conclusion was robust to the majority of sensitivity analyses undertaken.

Choice of second and third line treatments was more uncertain, but very potent corticosteroids, once or twice daily, were generally shown to be most cost effective followed by once daily two-compound formulation product. This conclusion was sensitive to alternative assumptions regarding suitability and acceptability of certain comparators.

- Sensitivity analyses in which continuous or consecutive use of topicals containing steroids was restricted found that once daily vitamin D or vitamin D analogue may be cost-effective as second or third line treatment in sequences with potent and very potent corticosteroids.
- Sensitivity analyses in which very potent corticosteroids were reserved for third line treatment showed that once daily vitamin D or vitamin D analogue or once daily two-compound formulation product may offer the best and second best value for NHS resources, respectively.
- Sensitivity analyses in which only once daily applications were considered found that initial treatment with potent steroids was optimal, followed by either very potent corticosteroid and then two-compound formulation product if steroids could be used continuously or followed by vitamin D or vitamin D analogue and very potent corticosteroid if continued use of steroids was to be avoided.

N.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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