Appendix L: Network meta-analysis of topical therapies in the treatment of scalp psoriasis

L.1 Clinical question

In people with scalp psoriasis: what are the clinical effectiveness, safety, tolerability and cost-effectiveness of available topical therapies?

L.2 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in Chapter 6) make it difficult to determine which intervention is most effective in the treatment of scalp psoriasis. The challenge of interpretation has arisen for two reasons:

- Some pairs of alternative strategies have not been directly compared in a randomised controlled trial (for example, very potent corticosteroid vs combined vitamin D analogue and potent corticosteroid)
- There are frequently multiple overlapping comparisons (for example vitamin D or vitamin D analogue vs potent corticosteroid, vitamin D or vitamin D analogue vs combined vitamin D analogue and potent corticosteroid and potent corticosteroid vs combined vitamin D analogue and potent corticosteroid) that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy, defined as the achievement of clearance or near clearance. The analysis also provides estimates of effect (with 95% credible interval) for each intervention compared to one another and compared to a single baseline risk. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness of the topical therapies in the original cost-effectiveness modelling (see Appendix N).

Conventional meta-analysis assumes that for a fixed effect analysis, the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same relative effect across all trials of intervention A compared to intervention B as it does across trials of intervention A versus intervention C, and so on. Thus, in a random effect network meta-analysis, the assumption is that intervention A has the same effect distribution across all trials of A versus B, A versus C and so on.

L.3 Methods

L.3.1 Study selection and data collection

To estimate the odds ratios and relative risks, we performed a NMA that simultaneously used all the relevant randomised controlled trial evidence from the clinical evidence review (presented in Chapter 6). As with conventional meta-analyses, this type of analysis does not break the

randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

The inclusion criteria and comparisons considered for the NMA were the same as in the clinical review (see Chapter 6).

The outcomes considered as part of the NMA were restricted to those measuring response:

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

Unfortunately, the network of evidence for the outcome of clear/nearly clear or marked improvement (at least 75% improvement) on the Patient's assessment of overall global improvement (PAGI) or clear/nearly clear/minimal (not mild) on Patient's Global Assessment was not connected such that an analysis could be performed.

As noted in the review of direct evidence, the preferred figures for the network meta-analysis were based on a modified available case analysis (whereby patients known to have dropped out due to lack of efficacy are included in the denominator for efficacy outcomes and those known to have dropped out due to adverse events are included in the numerator and denominator when analysing adverse events). This method was used rather than intention-to-treat analysis to avoid making assumptions about the participants for whom outcome data were not available.

However, when the data were presented as an ITT analysis in the study it was not possible to modify this to an available case analysis as insufficient detail was provided. This was the case in 10 studies[1-10].

L.3.2 Interventions

The interventions compared in the NMAs were those found in the randomised controlled trials included in the clinical evidence review (see Chapter 6). In order to reduce heterogeneity in the network, interventions were broken down by treatment frequency from the outset. In other words, once daily vitamin D or vitamin D analogue and twice daily vitamin D or vitamin D analogue were considered separate comparators in the NMA. Placebo/vehicle delivered once daily was also considered separately from twice daily placebo/vehicle.

The interventions included were

- Vehicle/Placebo once daily (OD)
- Vehicle/Placebo twice daily (BD)
- Vitamin D or vitamin D analogue OD
- Vitamin D or vitamin D analogue BD
- Potent corticosteroid OD
- Potent corticosteroid BD
- Very potent corticosteroid OD
- Very potent corticosteroid BD
- Combined vitamin D analogue and potent corticosteroid OD
- Coal tar polytherapy OD

L.3.3 Baseline risk

The baseline risk is defined here as a person's 'risk,' or probability, of achieving clearance or near clearance with no active treatment other than vehicle/placebo. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks.

Deriving the figure from our randomised controlled trials involved aggregating the number of patient's achieving 'clear' or 'nearly clear' across the vehicle/placebo arms of studies included in our NMA and dividing by the aggregate sample size from the same arms. Because there appeared to be a difference between the likelihood of response between once daily and twice daily vehicle/placebo, twice daily vehicle/placebo was chosen as the baseline comparator for both networks of evidence.

Using this method produced a baseline probability of 11.3% (95% CI: 8.1% to 14.5%) for achieving clearance or near clearance as measured by IAGI and PGA.

L.3.4 Statistical analysis

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

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. A diagram of the evidence network was produced (**Error! Reference source not found.**) and is presented in section **Error! Reference source not found.**.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo Simulation. As it was a Bayesian analysis, the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For each analysis, a series of 20,000 burn-in simulations were run to allow convergence and then a further 40,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (see Chapter 6). In preparation for the NMA, these conventional meta-analyses were re-run to produce odds ratios and these are presented as part of the NMA results section.

The outputs of the NMA were odds ratios. Odds ratios and their 95% credible intervals were generated for every possible pair of comparisons by combining direct and indirect evidence in the network. To be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation, relative risks were computed from the outputs of the NMA. Relative risks (RR) were derived from the odds ratios for each intervention compared back to a single 'no treatment' baseline risk, using the baseline risk as described above and the following formula:

$$RR = \frac{OR}{1 - P_0 (1 - OR)}$$

where P_o is the baseline risk.

We estimated the RR for each of the 40,000 simulations, treating P_o as a constant. The point estimate of the RR was taken to be the median of the 40,000 simulations and the 95% credible intervals for the RR were taken to be the 2.5th and 97.5th centiles from the distribution of the RR.

We also assessed the probability that each intervention was the best treatment by calculating the relative risk of each intervention compared to once daily vehicle/placebo, and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk. Using this same method, we also calculated the overall ranking of interventions according to their relative risk compared to once daily vehicle/placebo.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations (e.g. sex, age, baseline severity)
- Different interventions (e.g. product, dose, vehicle type)
- Different measures of outcome (different scales for IAGI and PGA; PAGI)
- Different follow-up periods (e.g. 2 weeks, 4 weeks, 6 weeks, 8 weeks)

This heterogeneity is a problem for network meta-analysis and should be dealt with by subgroup analysis and sometimes by re-defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed by comparing the odds ratios from the direct evidence (from pair-wise meta-analysis) to the odds ratios from the combined direct and indirect evidence (from NMA). We performed a significance test to determine whether the differences between estimates of effect from the pair-wise meta-analyses and network meta-analyses were statistically significant. No significant inconsistency was identified.

L.4 Results

A total of 13 studies[1-14] from the original evidence review met the inclusion criteria for the network. **Error! Reference source not found.** presents all the available data used in the analysis for investigator assessed outcomes. **Error! Reference source not found.** shows the network created by eligible comparisons for the NMA. Of the 55 possible pair-wise comparisons between the 10 interventions in the network, 14 have been compared directly in at least one trial.

Table 1: Study characteristics and IAGI/PGA and PAGI efficacy data used in networks

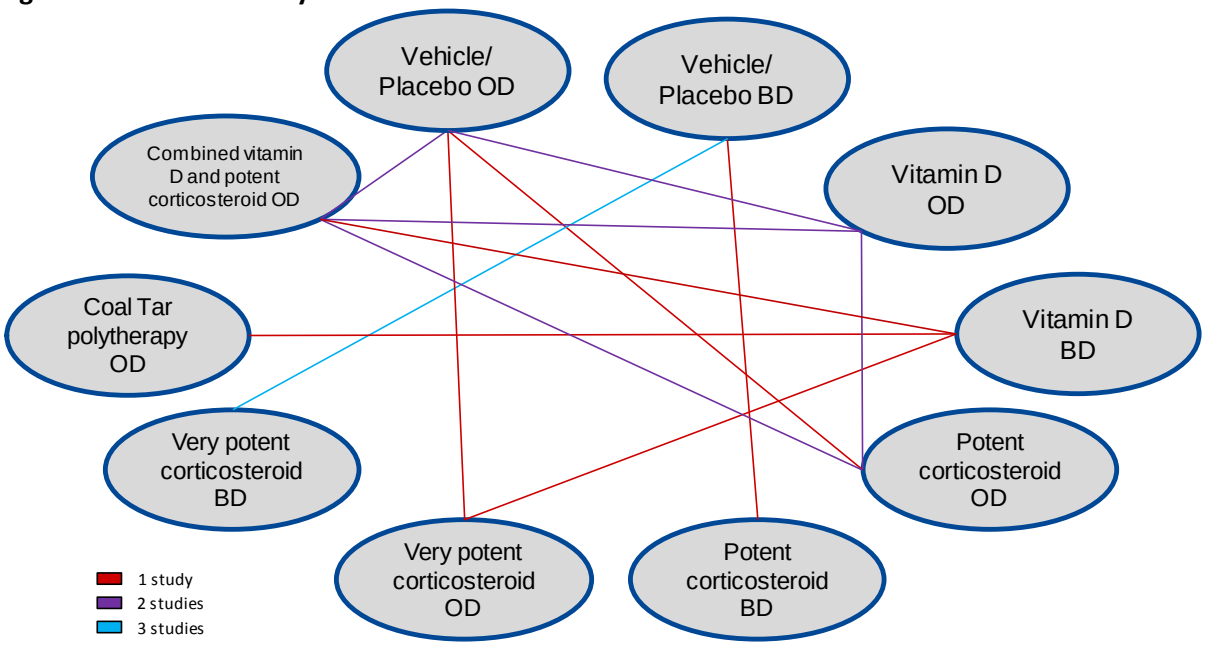
Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'		
			r	n	%
Franz 1999	Placebo	BD	12	57	21.1%
	Potent corticosteroid	BD	68	115	59.1%
Franz 2000	Placebo	BD	5	63	7.9%
	Very potent corticosteroid	BD	86	125	68.8%
Green 1994	Placebo	OD	4	24	16.7%
	Vitamin D or vitamin D analogue	OD	15	25	60.0%
Jarratt 2004	Placebo	OD	1	47	2.1%

Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'		
	Very potent corticosteroid	OD	40	95	42.1%
Jemec 2008	Placebo	OD	31	136	22.8%
	Vitamin D or vitamin D analogue	OD	100	272	36.8%
	Potent corticosteroid	OD	356	556	64.0%
	Combined vitamin D analogue and potent corticosteroid	OD	385	541	71.2%
Klaber 1994	Vitamin D or vitamin D analogue	BD	138	236	58.5%
	Potent corticosteroid	BD	175	232	75.4%
Kragballe 2009	Vitamin D or vitamin D analogue	BD	33	105	31.4%
	Combined vitamin D analogue and potent corticosteroid	OD	142	207	68.6%
McKinnon 2000	Vitamin D or vitamin D analogue	BD	120	210	57.1%
	Coal tar polytherapy	OD	79	213	37.1%
Olsen 1991	Placebo	BD	16	189	8.5%
	Very potent corticosteroid	BD	129	188	68.6%
Reygagne 2005	Vitamin D or vitamin D analogue	BD	21	75	28.0%
	Very potent corticosteroid	OD	38	76	50.0%
Sofen 2011	Placebo	BD	5	40	12.5%
	Very potent corticosteroid	BD	35	41	85.4%
Tyring 2010	Placebo	OD	17	42	40.5%
	Combined vitamin D analogue and potent corticosteroid	OD	97	135	71.9%
van de Kerkhof 2009	Vitamin D or vitamin D analogue	OD	124	286	43.4%
	Potent corticosteroid	OD	343	562	61.0%
	Combined vitamin D analogue and potent corticosteroid	OD	388	567	68.4%

L.4.1 Clear/nearly clear as measured by IAGI or PGA

Figure 1 presents all the interventions included in the NMA as well as shows where there is direct evidence for a particular comparison and the number of studies that have included that comparison. For example, there are 3 studies reporting the outcome 'clear' or 'nearly clear' as measured by IAGI or PGA for the comparison of twice daily vehicle/placebo and twice daily very potent corticosteroid. The diagram also highlights where there are gaps in the direct evidence. For example, there are no studies comparing combined vitamin D analogue and potent corticosteroid to very potent corticosteroid.

Figure 1: Clear or nearly clear – IAGI and PGA



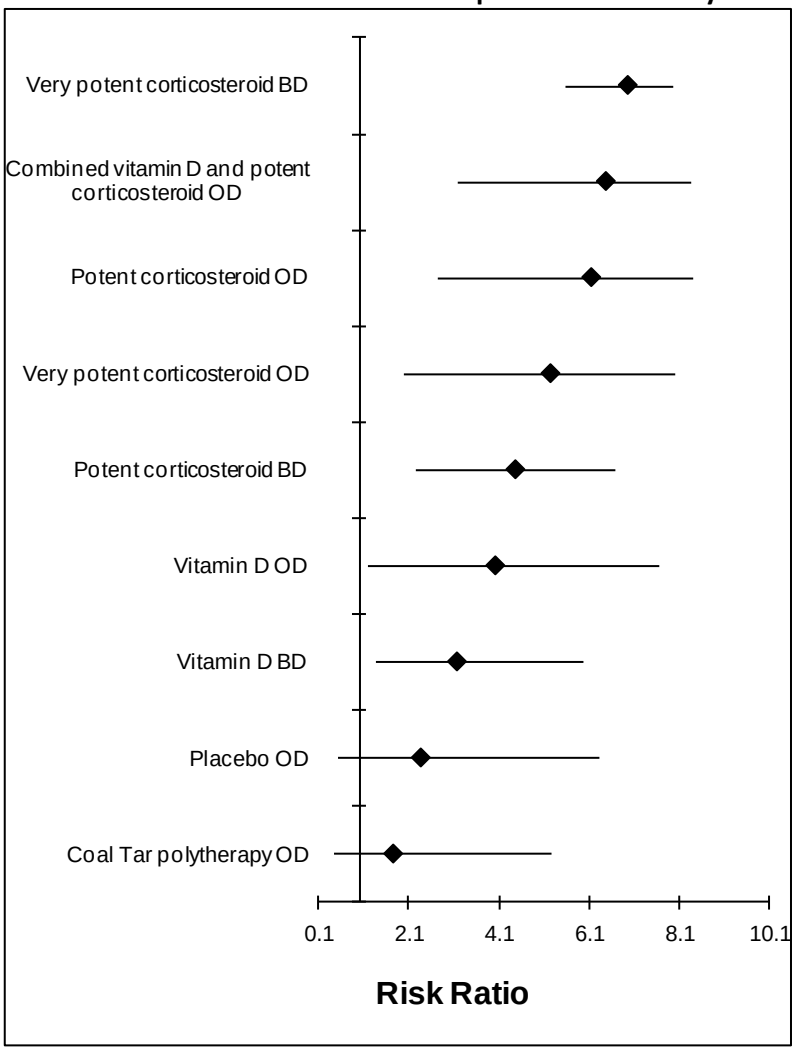
Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the analysis.

Error! Reference source not found. presents the relative risk of each intervention compared to twice daily vehicle/placebo. It also gives a probability that the intervention is the most effective overall. **Error! Reference source not found.** presents these estimates and their uncertainty as a forest plot.

Table 2: Relative risks of clear/nearly clear on IAGI/PGA for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower CrI	Upper CrI	Probability most effective
Very potent corticosteroid BD	6.946	5.583	7.962	59.0%
Combined vitamin D analogue and potent corticosteroid OD	6.459	3.18	8.365	22.3%
Potent corticosteroid OD	6.135	2.752	8.433	12.2%
Very potent corticosteroid OD	5.228	1.991	8.006	5.9%
Potent corticosteroid BD	4.448	2.255	6.702	0.4%
Vitamin D or vitamin D analogue OD	4.002	1.175	7.686	0.1%
Vitamin D or vitamin D analogue BD	3.149	1.364	5.993	0.0%
Placebo OD	2.345	0.5069	6.36	0.0%
Coal Tar polytherapy OD	1.732	0.4415	5.263	0.1%

Figure 2: Relative risks for all interventions compared to twice daily vehicle/placebo



Based on the relative risk estimates, it would appear that all active interventions with the exception of once daily coal tar polytherapy are more likely to induce clearance or near clearance than twice daily vehicle/placebo.

It is difficult to observe differences between active comparators based on the relative risk estimates presented in **Error! Reference source not found.** and **Error! Reference source not found.**. The NMA also produced odds ratios for every possible pair-wise comparison, regardless of whether they have been compared in a clinical trial. These estimates, presented in **Error! Reference source not found.**, indicate that there are very few comparisons for which the treatment effect reaches statistical significance.

A few notable exceptions include:

- Once daily potent corticosteroid is more effective than once and twice daily vitamin D or vitamin D analogue
- Once daily combined vitamin D analogue and potent corticosteroid is more effective than once and twice daily vitamin D or vitamin D analogue
- Twice daily very potent corticosteroid is more effective than vitamin D analogue applied twice daily

Once and twice daily application of all products containing steroids (potent, very potent and combined vitamin D analogue and potent corticosteroid) is more effective than once daily coal tar polytherapy.

Figure 3: Odds ratios for clear/nearly clear as measured by IAGI or PGA, results of conventional and network meta-analyses

Placebo OD		**2.29** **1.48 to 3.56**		**6.03** **3.90 to 9.33**		**33.45** **4.43 to 252.84**		**3.75** **1.82 to 7.72**	
0.354 0.05 to 2.096	Placebo BD				**5.43** **2.60 to 11.34**		**25.78** **16.00 to 41.53**		
2.697 **1.012 to 6.372**	**6.464** **1.202 to 50.7**	Vitamin D OD		**2.50** **2.00 to 3.03**				**3.43** **2.78 to 4.24**	
1.53 0.387 to 6.725	**4.329** **1.43 to 16.4**	0.6716 0.152 to 2.66	Vitamin D BD		**2.17** **1.47 to 3.23**	**2.56** **1.32 to 5.00**		**4.77** **2.87 to 7.90**	**0.44** **0.30 to 0.65**
6.212 **3.202 to 18.17**	**17.6** **3.539 to 148**	**2.697** **1.365 to 6.566**	**4.047** **1.155 to 19.59**	Potent corticosteroid OD				**1.39** **1.16 to 1.65**	
2.829 0.454 to 14.98	**7.908** **2.681 to 24.2**	1.234 0.18 to 5.954	1.839 0.595 to 4.536	0.4575 0.06 to 1.998	Potent corticosteroid BD				
3.992 0.622 to 28.1	**11.28** **2.278 to 72.1**	1.728 0.247 to 11.19	2.61 0.75 to 9.136	0.6386 0.08 to 3.702	1.42 0.325 to 7.969	Very potent corticosteroid OD			
10.14 **1.291 to 72.82**	**28.28** **13.34 to 68.3**	4.367 0.505 to 29.15	**6.558** **1.449 to 26.22**	1.603 0.17 to 9.916	3.614 0.937 to 14.38	2.527 0.348 to 15.5	Very potent corticosteroid BD		
7.4 **3.5 to 16.85**	**21.01** **4.396 to 128**	**3.239** **1.38 to 6.672**	**4.833** **1.464 to 15.99**	1.204 0.47 to 2.153	2.616 0.614 to 13.97	1.856 0.324 to 10.52	0.7389 0.123 to 5.053	Combined vitamin D and Potent corticosteroid OD	
0.6785 0.112 to 4.514	1.909 0.412 to 11.5	0.2973 0.044 to 1.769	0.4437 0.139 to 1.407	**0.1098** **0.01 to 0.585**	0.2399 0.059 to 1.268	**0.1705** **0.031 to 0.9295**	**0.0674** **0.011 to 0.466**	**0.092** **0.017 to 0.483**	Coal Tar polytherapy OD

Note: Results in the white area are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct evidence between the column-defined treatment compared to the row-defined treatment. Odds ratios greater than 1 favour the column-defined treatment. Results in grey are the median odds ratios and 95% credible intervals from the NMA of direct and indirect evidence between the row-defined treatment compared to the column-defined treatment. Odds ratios greater than 1 favour the row-defined treatment.

L.5 Discussion

Based on the results of conventional, pairwise meta-analyses of direct evidence, as has been previously presented in chapter 6, deciding upon the most effective topical for the treatment of moderate to severe psoriasis of the scalp is difficult. Many interventions have not been directly compared to one another in a randomised controlled trial and there are many instances of overlapping comparisons that could potentially give inconsistent estimates of effect. In order to overcome these challenges and to base decisions on a coherent set of treatment effects across all the trial evidence, a network meta-analysis was performed.

The NCGC analysis was based on a total of 13 studies, including 5,640 patients randomised to 10 different interventions. These studies formed a network of evidence on the effectiveness of topical therapies in achieving a physician or investigator assessed outcome of response (clear/nearly clear). An evaluation on a patient assessed response outcome was sought, but could not be undertaken because a single network could not be formed based on the available direct comparisons. The findings from the NMA fed into the original economic analysis of topical therapy sequences (see Appendix N), and helped to facilitate GDG decision-making about the optimal treatments for patients with moderate to severe psoriasis of the scalp.

Results of the NMA showed that all topicals with active agents (non-vehicle cream or ointment), except coal tar polytherapy, were more effective than placebo/vehicle. Twice daily very potent corticosteroid was shown to be the most effective topical therapy, followed closely by once daily two-compound formulation product (potent corticosteroid and vitamin D analogue). Products containing potent or very potent corticosteroids were more effective than products without corticosteroids; however, in this trend did not reach significance in most cases. Vitamin D or vitamin D analogues, although more effective than placebo, were among the least effective overall, only a bit better than coal tar polytherapy.

There was a non-significant trend towards once daily application of a given topical to be more effective than twice daily application. This was found for all agents except for very potent corticosteroids. This was directly opposite to the results of the NMA for the treatment of trunks and limbs in which twice daily was found to be more effective. The GDG thought that this may be a function of adherence and/or acceptability of twice daily scalp treatments. Their experience suggests that patients strongly prefer once daily scalp applications due to the messiness, inconvenience and cosmetic unacceptability of multiple applications each day.

The NMA was undertaken to synthesise estimates of efficacy for different topical therapies under consideration for the treatment of moderate to severe psoriasis of the scalp. The GDG considered response, in terms of the achievement of clearance or near clearance, to be the most important outcome from the clinical evidence review; however, other outcomes, namely those measuring safety, were also very important. They were aware that many of the most effective interventions, potent and very potent corticosteroids, are sometimes associated with certain adverse events (e.g. irreversible skin atrophy, rapid relapse, disease destabilisation) that may limit their utility in the long term management of patients with scalp psoriasis. In interpreting the evidence and making recommendations, the GDG relied on the efficacy results from the NMA as well as results for the other outcomes, particularly adverse events, included in the clinical evidence review of direct evidence.

L.6 WinBUGS code

#Random effects model for multi-arm trials (any number of arms)

```
model{
for (i in 1:NS)
                    {          Events[i] <- r[i,1]*equals(t[i,1],1)
                               Numpatients[i] <- n[i,1]*equals(t[i,1],1)
                    }
totEvents<-sum(Events[])
totNumpatients<-sum(Numpatients[])
BR<- totEvents/totNumpatients
for(i in 1:NS){
      w[i,1] <-0
            delta[i,t[i,1]]<-0
            mu[i] ~ dnorm(0,.0001)                                  # vague priors for 24 trial baselines
            for (k in 1:na[i])  {
                r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])                          # binomial likelihood
                              logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]          # model


#Deviance residuals for data i
     rhat[i,k] <- p[i,t[i,k]] * n[i,k]
     dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
                    }
          sdev[i]<- sum(dev[i,1:na[i]])
                     for (k in 2:na[i]) {
           delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])          # trial-specific LOR distributions
           md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]                # mean of LOR distributions
            taud[i,t[i,k]] <- tau *2*(k-1)/k                            #precision of LOR distributions
            w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])         #adjustment, multi-arm RCTs
            sw[i,k] <-sum(w[i,1:k-1])/(k-1) }              # cumulative adjustment for multi-arm trials
  }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }                  #  vague priors for basic parameters
```

```
sd~dunif(0,2)                                   #  vague prior for random effects standard deviation
tau<-1/pow(sd,2)
rr[1]<-1
for (k in 2:NT)  {logit(v[k])<-logit(BR)+d[k]
rr[k]<-v[k]/BR  }                          # calculate relative risk
sumdev <- sum(sdev[])                                          # Calculate residual deviance
# Ranking and prob{treatment k is best}
 for (k in 1:NT) {
            rk[k]<-NT+1-rank(rr[],k)
best[k]<-equals(NT+1-rank(rr[],k),1)}
# pairwise ORs and RRs
for (c in 1:(NT-1))
        {  for (k in (c+1):NT)
             {  lor[c,k] <- d[k] - d[c]
               log(or[c,k]) <- lor[c,k]
               lrr[c,k] <- log(rr[k]) - log(rr[c])
               log(rrisk[c,k]) <- lrr[c,k]
             }
         }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#        per trial in the dataset. In this dataset M is 5.


list(NS=13,NT=10)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 31 136 100 272 356 556 385 541 NA NA 2 3 5 9 NA 4
 1 47 40 95 NA 1 NA 1 NA NA 2 5 NA NA NA 2
 17 42 97 135 NA 1 NA 1 NA NA 2 9 NA NA NA 2
```

```
4 24 15 25 NA 1 NA 1 NA NA 1 4 NA NA NA 2

12 57 68 115 NA 1 NA 1 NA NA 1 6 NA NA NA 2

5 63 86 125 NA 1 NA 1 NA NA 1 8 NA NA NA 2

16 189 129 188 NA 1 NA 1 NA NA 1 8 NA NA NA 2

5 40 35 41 NA 1 NA 1 NA NA 1 8 NA NA NA 2

124 286 343 562 388 567 NA 1 NA NA 3 5 9 NA NA 3

138 236 175 232 NA 1 NA 1 NA NA 4 6 NA NA NA 2

21 75 38 76 NA 1 NA 1 NA NA 4 7 NA NA NA 2

33 105 142 207 NA 1 NA 1 NA NA 4 9 NA NA NA 2

120 210 79 213 NA 1 NA 1 NA NA 4 10 NA NA NA 2

END


list(

d=c(NA,0,0,0,0,0,0,0,0,0),

sd=.2,

mu=c(3,-1,-2,3,2,-1,2,-3,-1,2,-3,0,1),

delta = structure(.Data = c(NA,NA,0,NA,-1,NA,NA,NA,-3,NA,NA,NA,NA,NA,-
2,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,2,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,NA,
NA,NA,-3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
1,NA,NA,NA,NA,NA,NA,NA,NA,NA,-1,NA,NA,NA,NA,NA,NA,1,NA,NA,NA,-
1,NA,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,1,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,
NA,1,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-1

),.Dim=c(13 , 10))))
```

L.7 References

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