Appendix K: Network meta-analysis of topical therapies in the treatment of chronic plaque psoriasis

K.1 Clinical question

In people with chronic plaque psoriasis: what are the clinical effectiveness, safety, tolerability and cost-effectiveness of topical vitamin D or vitamin D analogues, potent or very potent corticosteroids, tar, dithranol and retinoids?

K.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 chronic plaque 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, concurrent vitamin D or vitamin D analogues and potent corticosteroid vs combined vitamin D or vitamin D analogues and potent corticosteroid)
- There are frequently multiple overlapping comparisons (for example vitamin D or vitamin D analogues vs potent corticosteroid, vitamin D or vitamin D analogues vs combined vitamin D or vitamin D analogues and potent corticosteroid and potent corticosteroid vs combined vitamin D or vitamin D analogues 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, the Bayesian equivalent of a confidence 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 M).

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.

K.3 Methods

K.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 for the NMA were the same as in the clinical review (section 6.1.1). Comparisons considered in the base case NMA were also the same as the clinical review, with a few exceptions. Two studies were excluded from the clinical review due to the comparators not meeting the protocol inclusion criteria; these have been included in a sensitivity analysis of the NMA. In addition, combined vitamin D or vitamin D analogues and potent corticosteroid administered twice daily was not considered a relevant comparator in the clinical review, but it has been included in the NMA as part of a sensitivity analysis.

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

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

Some included studies will have reported both outcomes, whereas some will have only included one or the other. For this reason, two networks of evidence were developed and analysed.

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 36 studies for efficacy outcomes. In the remaining 14 studies ACA figures as reported in the paper were used{Molin, 1997 MOLIN1997A /id;Kragballe, 1991 KRAGBALLE1991 /id;Highton, 1995 HIGHTON1995 /id;Dubertret, 1992 DUBERTRET1992 /id;Harrington, 1996 HARRINGTON1996 /id;Langley, 2011 LANGLEY2011A /id;Medansky, 1987 MEDANSKY1987 /id;Sears, 1997 SEARS1997 /id;Katz, 1991 KATZ1991 /id;Weinstein, 1997 WEINSTEIN1997 /id;Weinstein, 1996 WEINSTEIN1996 /id;Gottlieb, 2003 GOTTLIEB2003C /id;Berth-Jones, 1992 BERTHJONES1992 /id;Alora-Palli, 2010 ALORAPALLI2010 /id;Pinheiro, 1997 PINHEIRO1997 /id}. However, it was still possible to use a modified available case analysis for withdrawal outcomes for most studies, apart from in one study where data were taken from the Cochrane review, which reported on the ITT population {Barker, 1999 BARKER1999A /id} , and one study for which withdrawals were not reported by group{Kragballe, 1991 KRAGBALLE1991 /id}.

K.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 analogues and twice daily vitamin D or vitamin D analogues 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 or vitamin D analogues and potent corticosteroid OD
- Concurrent vitamin D or vitamin D analogues and potent corticosteroid (morning and evening application, respectively)
- Retinoid OD (tazarotene)
- Coal tar OD
- Coal tar BD
- Dithranol OD

K.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 12.5% (95% CI: 10.4% to 14.6%) for achieving clearance or near clearance as measured by IAGI and PGA.

Using this method produced a baseline probability of 14.4% (95% CI: 11.7% to 17.0%) for achieving clearance or near clearance as measured by PAGI.

K.3.4 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS19. We adapted a multi-arm random effects model template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between arms in trials with any number of trial arms. The code can be found towards the end of this appendix (K.7)

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. For each population and

outcome subgroup, a diagram of the evidence network was produced (Figure 1 and Figure 4) and is presented in section K.4.

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 in the direct evidence, caused by heterogeneity, was assessed using Bucher's method, comparing the odds ratios from the pairwise meta-analysis wherever a loop of direct evidence was available. We also explored inconsistency 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 using either method was identified.

K.4 Results

A total of 38 studies{Alora-Palli, 2010 ALORAPALLI2010 /id;Barker, 1999 BARKER1999A /id;Berth-Jones, 1992 BERTHJONES1992 /id;Camarasa, 2003 CAMARASA2003 /id;Christensen, 1999 CHRISTENSEN1999 /id;Cunliffe, 1992 CUNLIFFE1992 /id;Decroix, 2004 DECROIX2004 /id;Douglas, 2002 DOUGLAS2002 /id;Fleming, 2010 FLEMING2010A /id;Gottlieb, 2003 GOTTLIEB2003C /id;Guenther, 2002 GUENTHER2002 /id;Highton, 1995 HIGHTON1995 /id;Hutchinson, 2000 HUTCHINSON2000 /id} from the original evidence review met the inclusion criteria for the base case in at least one network - 35 studies for the IAGI/PGA network and 14 for the PAGI network. An additional 3 studies{Menter, 2009 MENTER2009A /id;Oranje, 1997 ORANJE1997 /id;Thawornchaisit, 2007 THAWORNCHAISIT2007 /id}were included in the IAGI/PGA network sensitivity analysis and an additional 2 studies{Oranje, 1997 ORANJE1997 /id;Papp, 2003 PAPP2003 /id} were included in the PAGI network sensitivity analysis. Table 1 presents all the available data used in the base case analysis for both investigator and patient assessed outcomes. Figure 1 and Figure 4 show the 2 networks created by eligible comparisons for each NMA. Of the 105 possible pair-wise comparisons between the 14 interventions in the networks, 22 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'			PAGI 'clear/nearly clear'		
			r	n	%	r	n	%
Barker, 1999	Placebo	OD	1	26	3.8			
	Vitamin D	OD	13	28	46.4			
Perez, 1996	Placebo	OD	0	84	0.0			
	Vitamin D	OD	37	84	44.0			
Fleming, 2010	Placebo	OD	0	40	0.0			
	Vitamin D	OD	9	79	11.4			
	Potent corticosteroid	OD	14	83	16.9			
	Combined vitamin D and potent corticosteroid	OD	44	162	27.2			
Kaufmann, 2002	Placebo	OD	16	157	10.2	15	157	9.6
	Vitamin D	OD	107	480	22.3	137	480	28.5
	Potent corticosteroid	OD	176	476	37.0	216	476	45.4
	Combined vitamin D and potent corticosteroid	OD	276	490	56.3	316	490	64.5
Langley, 2011	Placebo	OD	5	91	5.5	14	64	21.9
	Vitamin D	OD	33	184	17.9	35	163	21.5

Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'			PAGI 'clear/nearly clear'		
	Combined vitamin D and potent corticosteroid	OD	73	183	39.9	69	171	40.4
Medansky, 1997	Placebo	OD	7	45	15.6			
	Potent corticosteroid	OD	18	50	36.0			
Katz, 1991	Placebo	OD	7	44	15.9			
	Potent corticosteroid	OD	27	46	58.7			
Decroix, 2004	Placebo	OD	5	33	15.2			
	Very potent corticosteroid	OD	144	189	76.2			
Weinstein Study A, 2003	Placebo	OD	7	229	3.1			
	Retinoid	OD	24	439	5.5			
Weinstein study B, 2003	Placebo	OD	2	214	0.9			
	Retinoid	OD	26	421	6.2			
Langner, 1992	Placebo	BD	9	29	31.0			
	Vitamin D	BD	21	29	72.4			
Langner, 1993	Placebo	BD	13	32	40.6			
	Vitamin D	BD	24	32	75.0			
Highton, 1995	Placebo	BD	23	123	18.7			
	Vitamin D	BD	87	124	70.2			
Dubertret, 1992	Placebo	BD	11	62	17.7			
	Vitamin D	BD	46	62	74.2			
Harrington, 1996	Placebo	BD				13	71	18.3
	Vitamin D	BD				148	291	50.9
Oranje, 1997(a)	Placebo	BD	15	43	34.9	16	34	47.1
	Vitamin D	BD	26	43	60.5	21	43	48.8
Papp, 2003(b)	Placebo	BD	8	107	7.5	13	107	12.1
	Vitamin D	BD	103	308	33.4	99	308	32.1
	Potent corticosteroid	BD	174	312	55.8	195	312	62.5
	Combined vitamin D and potent corticosteroid	BD (c)	229	301	76.1	223	301	74.1
Guenther, 2002	Placebo	BD	19	206	9.2	26	206	12.6
	Vitamin D	BD	115	227	50.7	117	227	51.5
	Combined vitamin D and potent corticosteroid	OD	95	150	63.3	98	150	65.3
	Combined vitamin D and potent corticosteroid	BD (c)	172	234	73.5	164	234	70.1
Wortzel, 1975	Placebo	BD	4	37	10.8			
	Potent corticosteroid	BD	15	39	38.5			
Sears, 1997	Placebo	BD	1	83	1.2	2	83	2.4
	Potent corticosteroid	BD	12	78	15.4	12	78	15.4
Lowe, 2005	Placebo	BD	0	29	0.0			
	Very potent corticosteroid	BD	84	162	51.9			

Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'			PAGI 'clear/nearly clear'		
Gottlieb, 2003	Placebo	BD	27	125	21.6	36	140	25.7
	Very potent corticosteroid	BD	85	120	70.8	79	139	56.8
Lebwohl, 2002	Placebo	BD	1	20	5.0	1	20	5.0
	Very potent corticosteroid	BD	10	61	16.4	8	61	13.1
Jarratt, 2006	Placebo	BD	2	60	3.3			
	Very potent corticosteroid	BD	47	60	78.3			
Kragballe, 1998	Vitamin D	OD	49	172	28.5	46	172	26.7
	Vitamin D	BD	69	172	40.1	69	172	40.1
	Concurrent vitamin D and potent corticosteroid		73	172	42.4	89	174	51.1
Ortonne, 2004	Vitamin D	OD	43	252	17.1	44	252	17.5
	Combined vitamin D and potent corticosteroid	OD	143	249	57.4	135	249	54.2
Camarasara, 2003	Vitamin D	BD	67	128	52.3			
	Potent corticosteroid	BD	81	130	62.3			
Molin, 1997	Vitamin D	BD	119	205	58.0			
	Potent corticosteroid	BD	116	207	56.0			
Kragballe, 1991	Vitamin D	BD				281	342	82.2
	Potent corticosteroid	BD				237	342	69.3
Cunliffe, 1992	Vitamin D	BD				123	201	61.2
	Potent corticosteroid	BD				101	200	50.5
Douglas, 2002	Vitamin D	BD	142	365	38.9	140	365	38.4
	Potent corticosteroid	BD	169	363	46.6	183	363	50.4
	Combined vitamin D and potent corticosteroid	BD (c)	251	369	68.0	248	369	67.2
Ruzicka, 1998	Vitamin D	BD	22	49	44.9			
	Concurrent vitamin D and potent corticosteroid		27	39	69.2			
Tham, 1994	Vitamin D	BD	13	27	48.1			
	Coal Tar	OD	3	27	11.1			
Alora-Palli, 2010	Vitamin D	BD	6	28	21.4			
	Coal Tar	BD	14	27	51.9			
Pinheiro, 1997	Vitamin D	BD	47	65	72.3			
	Coal Tar	BD	28	57	49.1			
Hutchinson, 2000	Vitamin D	BD	23	60	38.3			
	Dithranol	OD	24	54	44.4			
Wall, 1998	Vitamin D	BD	92	153	60.1	93	153	60.8
	Dithranol	OD	67	131	51.1	65	131	49.6
Berth-Jones, 1992	Vitamin D	BD	180	231	77.9	180	231	77.9
	Dithranol	OD	116	227	51.1	123	227	54.2
Christensen,	Vitamin D	BD	6	89	6.7			

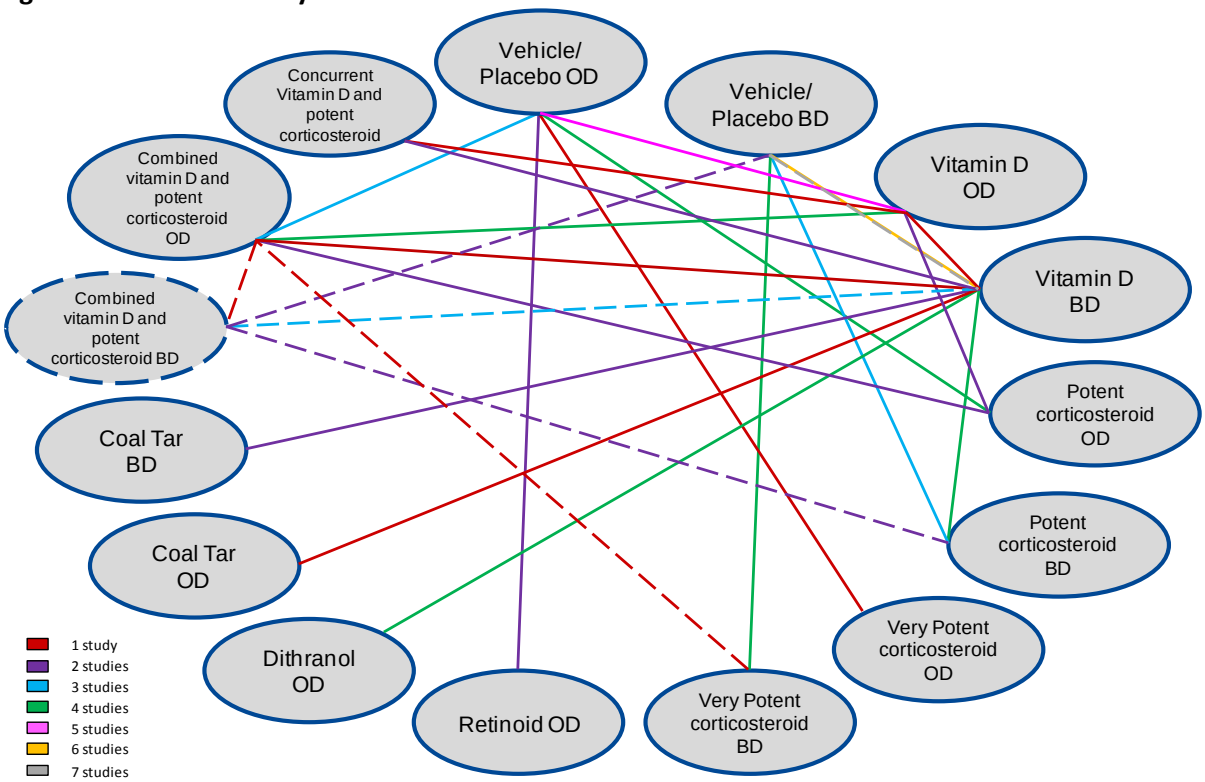
Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'			PAGI 'clear/nearly clear'		
1999	Dithranol	OD	4	77	5.2			
Thawornchaisit, 2007 (d)	Potent corticosteroid	BD	23	30	76.7			
	Coal Tar	BD	7	28	25.0			
Menter, 2009 (e)	Very potent corticosteroid	BD	32	44	72.7			
	Combined vitamin D and potent corticosteroid	OD	32	49	65.3			

(a) Oranje 1997 evaluated treatments in a paediatric population.
(b) Data from Papp 2003 for IAGI/PGA was included in the base case, but PAGI data was only included in the sensitivity analysis because it was excluded from the clinical review of direct evidence given that in the paper it was reported graphically.
(c) Twice daily combined vitamin D and potent corticosteroid was only included as a comparator in the sensitivity analysis given that it is currently unlicensed in the UK at this dose.
(d) The protocol for the clinical review of direct evidence included only comparisons of single topical therapies to either placebo/vehicle or vitamin D; therefore, the comparison of potent corticosteroid and coal tar was included only in the sensitivity analysis.
(e) The protocol for the clinical review of direct evidence included only comparisons of combination therapies to either vitamin D or potent corticosteroid; therefore, the comparison of combined vitamin D and potent corticosteroid and very potent corticosteroid was included only in the sensitivity analysis.

K.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 7 studies reporting the outcome 'clear' or 'nearly clear' as measured by IAGI or PGA for the comparison of twice daily vehicle/placebo and twice daily vitamin D or vitamin D analogues. The diagram also highlights where there are gaps in the direct evidence. For example, there are no studies comparing combined vitamin D or vitamin D analogues and potent corticosteroid to concurrent vitamin D or vitamin D analogues and 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 base case. Dashed lines indicate all head-to-head comparisons included in the sensitivity analysis.

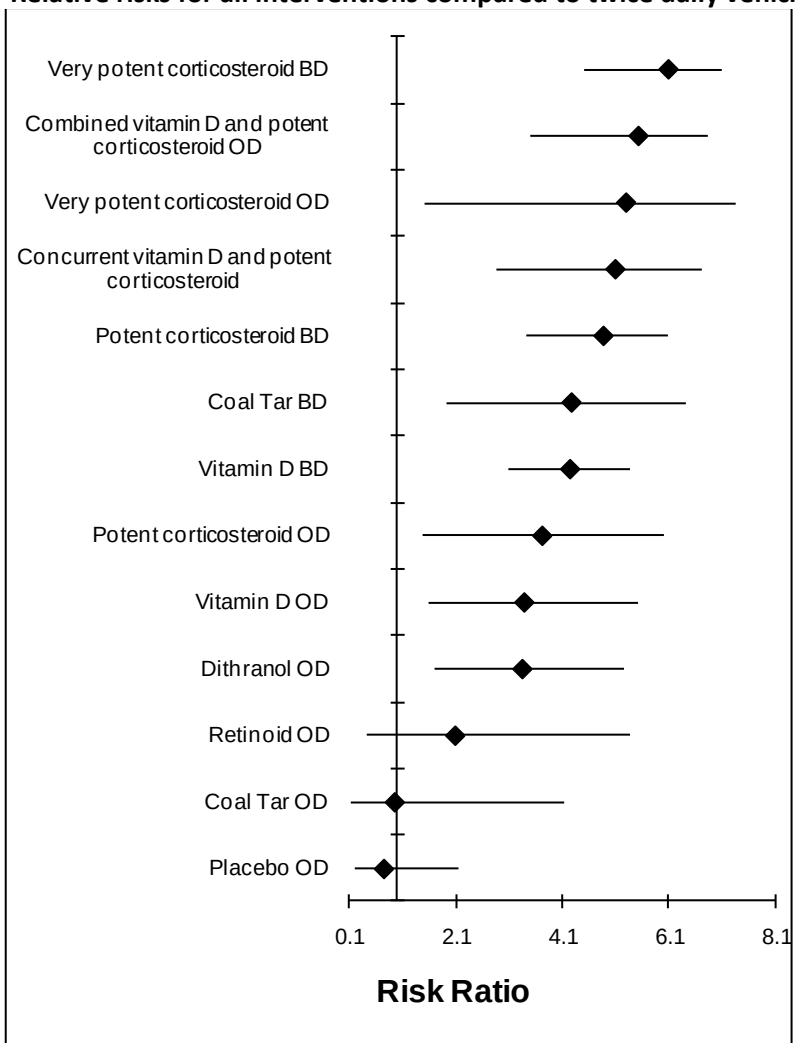
Table 2 presents the relative risk of each intervention compared to once daily vehicle/placebo. It also gives a probability that the intervention is the most effective overall. Figure 2 presents these estimates and their uncertainty as a forest plot.

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

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective
Very potent corticosteroid BD	6.095	4.507	7.102	48.5%
Combined vitamin D and potent corticosteroid OD	5.533	3.488	6.824	12.8%
Very potent corticosteroid OD	5.302	1.495	7.369	25.6%
Concurrent vitamin D and potent corticosteroid	5.1	2.863	6.726	7.7%
Potent corticosteroid BD	4.877	3.435	6.093	1.8%
Coal Tar BD	4.279	1.924	6.426	3.1%
Vitamin D or vitamin D analogue BD	4.251	3.074	5.368	0.0%
Potent corticosteroid OD	3.73	1.469	6.006	0.1%
Vitamin D or vitamin D analogue OD	3.393	1.586	5.529	0.0%
Dithranol OD	3.357	1.688	5.266	0.1%
Tazarotene OD	2.099	0.4376	5.387	0.1%
Coal Tar OD	0.9658	0.1153	4.127	0.1%

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective
Placebo OD	0.7629	0.2107	2.162	0.0%

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 exceptions of once daily coal tar and once daily retinoid are more likely to induce clearance or near clearance than twice daily vehicle/placebo. Twice daily vehicle/placebo appears to perform slightly better than once daily, but the effect is not statistically significant.

It is difficult to observe differences between active comparators based on the relative risk estimates presented in Table 2 and Figure 2. The NMA also produced odds ratios for every possible pair-wise comparison, regardless of whether they have been compared directly in a clinical trial. These estimates, presented in Figure 3, indicate that there are very few comparisons for which the treatment effect reaches statistical significance.

A few exceptions include:

- Twice daily very potent corticosteroid and once daily combined vitamin D or vitamin D analogues and potent corticosteroid are more effective than once daily vitamin D or vitamin D analogues

- Once daily combined vitamin D or vitamin D analogues and potent corticosteroid is more effective than once daily potent corticosteroid and once daily retinoid
- Twice daily very potent corticosteroid is more effective than once daily retinoid and once daily dithranol
- Twice daily vitamin D or vitamin D analogues, twice daily potent corticosteroids, twice daily very potent corticosteroids, combined and concurrent vitamin D or vitamin D analogues and potent corticosteroids are all more effective than once daily coal tar

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

Placebo OD		**4.82** **3.12 to 7.44**		**5** **3.12 to 8.01**		**17.92** **6.54 to 49.14**		**2.98** **1.45 to 6.12**	**12.11** **7.56 to 19.39**				
1.357 0.383 to 5.302	Placebo BD		**8.6** **6.34 to 11.67**		**12.47** **6.81 to 22.85**		**14.67** **8.84 to 24.34**		***17*** ***9.55 to 30.3***				
7.142 **3.395 to 17.41**	**5.262** **1.737 to 16.9**	Vitamin D OD	**1.69** **1.08 to 2.63**	**2.00** **1.52 to 2.63**					**4.44** **3.63 to 5.43**	**2.95** **1.89 to 4.61**			
11.12 **3.434 to 40.63**	**8.214** **4.441 to 15.3**	1.56 0.54 to 4.323	Vitamin D BD		**1.54** **1.28 to 1.82**				**1.76** **1.37 to 2.26**	**1.98** **1.41 to 2.76**	**0.13** **0.03 to 0.56**	0.78 0.43 to 1.39	**0.51** **0.39 to 0.67**
8.486 **3.79 to 19.88**	**6.27** **1.579 to 23.4**	1.185 0.466 to 2.737	0.763 0.203 to 2.623	Potent corticosteroid OD					**2.15** **1.69 to 2.73**				
15.65 **4.118 to 66.48**	**11.49** **5.379 to 25**	2.186 0.632 to 7.305	1.403 0.727 to 2.727	1.833 0.46 to 7.985	Potent corticosteroid BD							***0.10*** ***0.03 to 0.34***	
19.91 **3.553 to 121.3**	**14.67** **1.614 to 135**	2.783 0.378 to 19.4	1.791 0.205 to 15.61	2.344 0.34 to 17.35	1.276 0.132 to 12.13	Very potent corticosteroid OD							
33.77 **6.961 to 201.1**	**25** **9.4 to 75.3**	**4.754** **1.054 to 22.59**	3.047 0.966 to 10.69	3.996 0.79 to 23.73	2.171 0.635 to 8.227	1.71 0.153 to 20.98	Very potent corticosteroid BD		0.71 0.29 to 1.71				
3.425 **1.005 to 12.59**	2.508 0.404 to 15.4	0.4767 0.106 to 2.066	0.3078 0.052 to 1.751	0.4036 0.09 to 1.854	0.2199 0.033 to 1.375	0.1716 0.019 to 1.523	**0.101** **0.01 to 0.782**	Retinoid OD					
22.96 **10.14 to 57.01**	**16.92** **5.531 to 50.3**	**3.215** **1.563 to 6.211**	2.062 0.726 to 5.703	**2.703** **1.13 to 6.732**	1.471 0.427 to 4.89	1.156 0.158 to 8.336	0.6737 0.14 to 2.919	**6.72** **1.454 to 30.99**	Combined vitamin D and Potent corticosteroid OD				
17.65 **4.521 to 81.47**	**13.03** **3.958 to 44.8**	2.473 0.729 to 8.514	1.585 0.56 to 4.739	2.086 0.51 to 9.543	1.131 0.334 to 4.085	0.886 0.093 to 9.233	0.5201 0.1 to 2.494	5.147 0.788 to 36.01	0.7693 0.217 to 2.906	Concurrent vitamin D and Potent corticosteroid			
1.297 0.114 to 14.21	0.961 0.102 to 7.7	0.1813 0.016 to 1.696	**0.117** **0.014 to 0.863**	0.1528 0.01 to 1.707	**0.083** **0.009 to 0.684**	0.06407 0.003 to 1.246	**0.038** **0 to 0.377**	0.3806 0.024 to 5.559	**0.057** **0.005 to 0.535**	**0.073** **0.006 to 0.708**	Coal Tar OD		
11.32 **2.167 to 69.22**	**8.334** **2.23 to 33**	1.579 0.33 to 7.899	1.015 0.314 to 3.457	1.334 0.25 to 8.176	0.7262 0.189 to 2.964	0.566 0.049 to 7.084	0.3331 0.06 to 1.776	3.293 0.414 to 28.48	0.494 0.107 to 2.495	0.6403 0.131 to 3.203	8.759 0.873 to 106.3	Coal Tar BD	
7.007 **1.719 to 33.01**	**5.163** **1.88 to 14.4**	0.9773 0.263 to 3.636	0.6278 0.283 to 1.42	0.8206 0.19 to 3.972	0.448 0.16 to 1.297	0.3516 0.035 to 3.54	**0.2073** **0.05 to 0.836**	2.046 0.304 to 14.66	0.3043 0.084 to 1.16	0.3966 0.102 to 1.498	5.377 0.623 to 54.9	0.6215 0.143 to 2.57	Dithranol 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.

In terms of the probability of being most effective, in nearly half of all simulations (49%), twice daily very potent corticosteroid emerges as the most effective topical. In a further 26% of simulations, once daily very potent corticosteroid emerged as the most effective topical. This means that in nearly 75% of all simulations, very potent corticosteroids were the most effective topical among all topical therapies evaluated. Combined and concurrent vitamin D or vitamin D analogues and potent corticosteroid were most effective in 13% and 8% of simulations, respectively.

In addition to the probability that a given treatment is most effective, the network meta-analysis also provides an indication of the overall rank of topical treatments in terms of their relative effectiveness. This statistic gives us an indication of the confidence we might have in a particular treatment being among the best or among the worst relative to the other treatments available. For example, the results show us that once and twice daily vehicle/placebo are consistently the least effective topical therapies, never ranking better than between least and 3rd least effective.

As for active treatments, the results indicate that with the exception of very potent corticosteroid and combined vitamin D or vitamin D analogues and potent corticosteroid, once daily application of any topical ranks far lower in terms of effectiveness than twice daily application of any topical. In other words, once daily application of potent corticosteroid, vitamin D or vitamin D analogue, dithranol, retinoid and coal tar were consistently among the least effective topical interventions.

Once daily application of very potent corticosteroid and twice daily application of potent corticosteroid, vitamin D or vitamin D analogues and coal tar all rank consistently in the middle of all 14 comparators (i.e. 4th, to 7th most effective). They are neither the most effective nor the least effective.

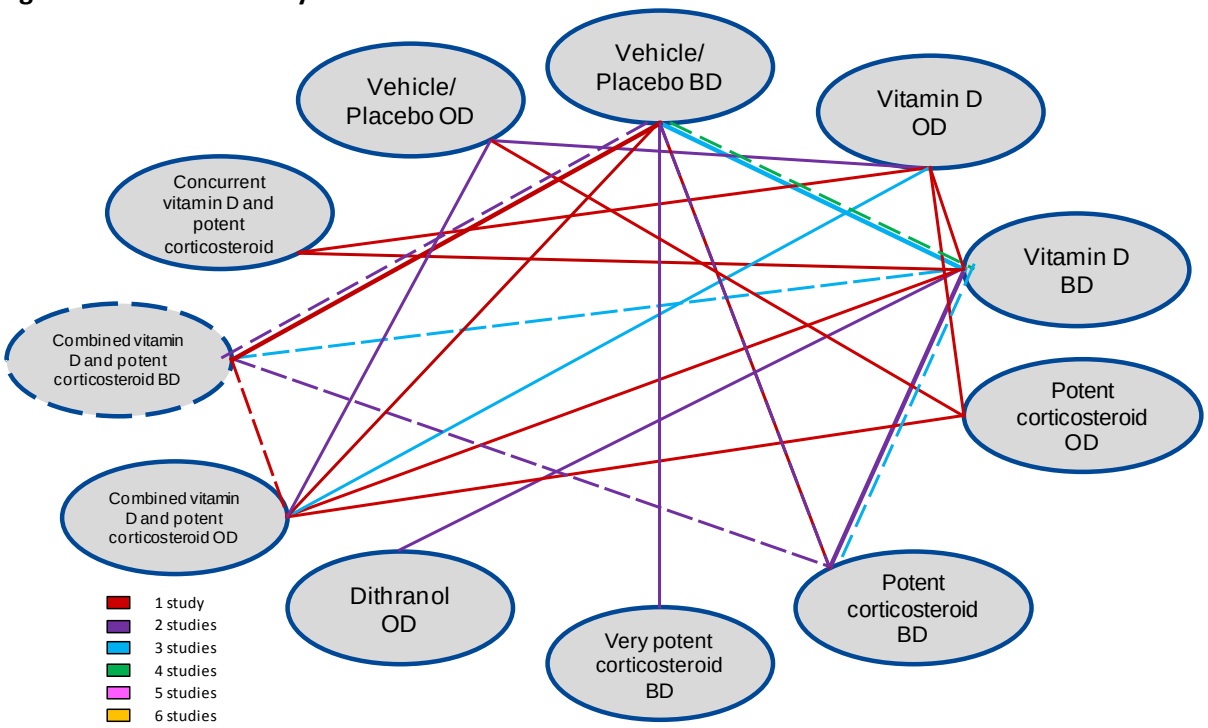
As indicated by the high relative risks for twice daily very potent corticosteroid and combined or concurrent vitamin D or vitamin D analogues and potent corticosteroid, these were consistently ranked among the most effective (i.e. most to 3rd most effective).

The residual deviance of the base case model was 85.23, with the number of unconstrained data points being 78. The closeness of these values indicates a reasonably good model fit. No significant inconsistency was identified between the odds ratios generated from pairwise meta-analyses of the available direct evidence and the odds ratios generated from the network meta-analyses of direct and indirect comparisons. However, some of the point estimates were somewhat different between the pairwise and network analyses. Notably the odds ratio for combined treatment versus *once daily* placebo was 12.1 in the pair-wise analysis and 22.9 in the network analysis. We can offer two explanations for this. First, the sample odds ratio from the Fleming 2010 trial is infinite (since there were zero events in the placebo arm. For the pair-wise analysis, RevMan would have added 0.5 to each cell, whereas the network meta-analysis being in the form of a logistic regression does not need to make such an assumption. Second indirect evidence within the network points to a larger effect size; for example the Guenter 2002 trial indicates an odds ratio for combined vs *twice daily* placebo of 17.0, implying an even bigger odds ratio compared to *once daily* placebo. For these reasons the credible interval from the network meta-analysis was wider than the confidence interval from the pairwise comparison.

K.4.2 Clear/nearly clear as measured by PAGI

Figure 4 presents all the interventions included in the NMA as well as shows where there is direct evidence for a particular comparison and the number of studies that have included that comparison. From the diagram, one can see that fewer studies have reported PAGI. There are 4 studies reporting the outcome of 'clear' or 'nearly clear' as measured by PAGI (in contrast to 7 studies reporting for IAGI or PGA) for the comparison of twice daily vehicle/placebo and twice daily vitamin D or vitamin D analogues.

Figure 4: Clear or nearly clear - PAGI



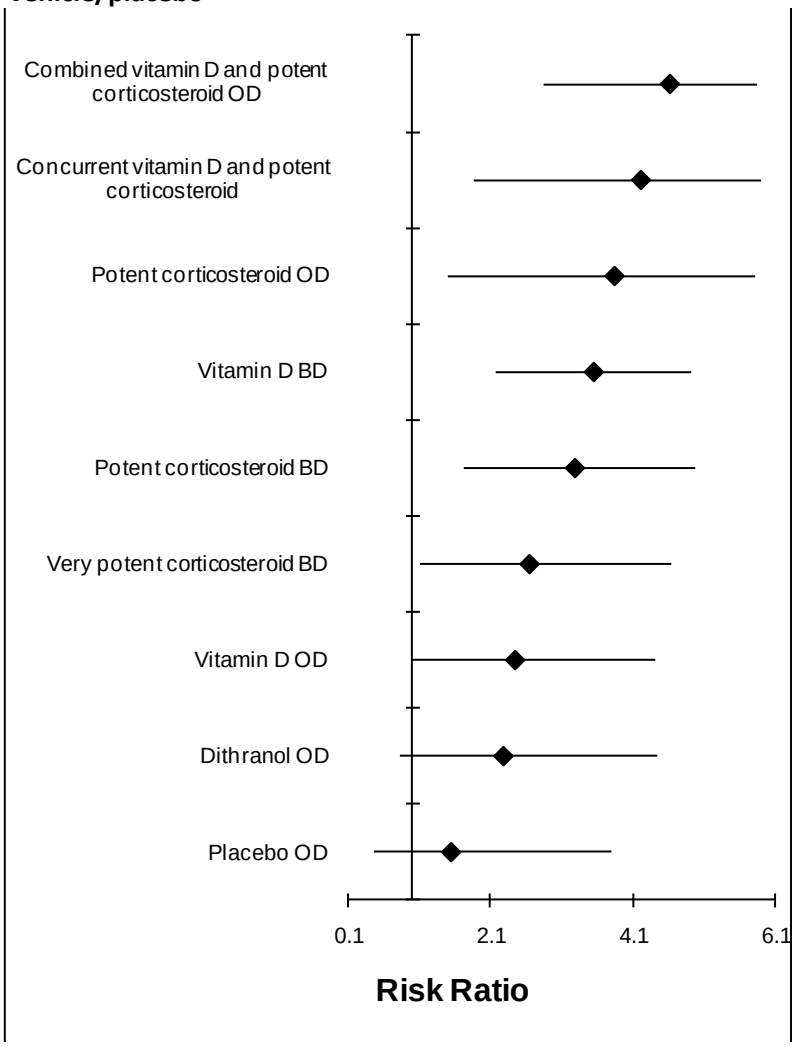
Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the base case. Dashed lines indicate all head-to-head comparisons included in the sensitivity analysis.

Table 3 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. Figure 5 presents these estimates and their uncertainty as a forest plot.

Table 3: Relative risks of clear/nearly clear with PAGI for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective
Combined vitamin D and potent corticosteroid OD	4.632	2.856	5.861	51.54%
Concurrent vitamin D and potent corticosteroid	4.224	1.854	5.915	27.64%
Potent corticosteroid OD	3.852	1.504	5.823	12.24%
Vitamin D or vitamin D analogue BD	3.56	2.161	4.922	1.57%
Potent corticosteroid BD	3.294	1.73	4.967	2.80%
Very potent corticosteroid BD	2.654	1.092	4.649	3.69%
Vitamin D or vitamin D analogue OD	2.451	0.9893	4.428	0.01%
Dithranol OD	2.287	0.8306	4.436	0.50%
Placebo OD	1.549	0.4531	3.798	0.01%

Figure 5: Relative risks of clear/nearly clear on PAGI for all interventions compared to twice daily vehicle/placebo



Based on the relative risk estimates, it would appear that all active interventions are more likely to induce clearance or near clearance than twice daily vehicle/placebo, although the results for once daily dithranol and once daily vitamin D or vitamin D analogues fail to reach statistical significance. A slightly counterintuitive finding is that once daily vehicle/placebo appears to perform slightly better than twice daily when using the patient reported outcome measure, but the effect is not statistically significant.

It is difficult to observe differences between active comparators based on the relative risk estimates presented in Table 3 and Figure 5. 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 indicate that there are only two comparisons between active agents for which the treatment effect reaches statistical significance: Once daily combined vitamin D or vitamin D analogues and potent corticosteroid is more effective than once daily vitamin D or vitamin D analogues and more effective than once daily dithranol.

Figure 6: Odds ratios for clear/nearly clear as measured by PAGI, results of conventional and network meta-analyses

Placebo OD		**2.39** **1.56 to 3.67**		**7.86** **4.48 to 13.79**			***8.31*** ***5.51 to 12.54***		
0.583 0.133 to 2.42	Placebo BD		**6.16** **4.18 to 9.09**		**7.36** **1.59 to 34.07**	**3.73** **2.27 to 6.12**	***13.05*** ***7.67 to 22.19***		
1.922 0.707 to 5.088	3.296 0.987 to 11.2	Vitamin D OD	**1.85** **1.16 to 2.86**	**2.08** **1.59 to 2.70**			**4.47** **3.64 to 5.48**	**2.87** **1.83 to 4.50**	
3.793 1.0 to 13.79	**6.495** **2.717 to 16**	1.976 0.708 to 5.563	Vitamin D BD		1.18 0.93 to 1.47		**1.77** **1.16 to 2.71**	**1.56** **1.02 to 2.39**	**0.44** **0.32 to 0.60**
4.545 **1.262 to 16.32**	**7.757** **1.651 to 39.1**	2.36 0.726 to 7.978	1.193 0.282 to 5.337	Potent corticosteroid OD			**2.19** **1.69 to 2.83**		
3.219 0.719 to 14.34	**5.535** **1.985 to 16.6**	1.683 0.499 to 6.042	0.8542 0.414 to 1.791	0.7144 0.14 to 3.549	Potent corticosteroid BD				
2.2 0.314 to 14.1	**3.748** **1.11 to 13.1**	1.144 0.204 to 6.446	0.5785 0.128 to 2.569	0.4831 0.06 to 3.55	0.6755 0.134 to 3.399	Very potent corticosteroid BD			
7.556 **2.769 to 19.96**	**12.9** **4.247 to 41.2**	**3.942** **1.891 to 8.057**	1.988 0.73 to 5.467	1.671 0.49 to 5.333	2.337 0.687 to 7.792	3.452 0.647 to 18.62	Combined vitamin D and Potent corticosteroid OD		
5.738 **1.159 to 27.28**	**9.799** **2.183 to 44.6**	2.986 0.803 to 10.92	1.509 0.417 to 5.465	1.261 0.22 to 6.91	1.768 0.4 to 7.72	2.606 0.368 to 18.65	0.7582 0.18 to 3.02	Concurrent vitamin D and Potent corticosteroid	
1.727 0.329 to 8.594	2.959 0.807 to 11.3	0.8999 0.22 to 3.705	0.4566 0.174 to 1.2	0.3825 0.07 to 2.182	0.5352 0.158 to 1.786	0.7911 0.13 to 4.779	**0.2286** **0.06 to 0.936**	0.3026 0.06 to 1.551	Dithranol 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.

In terms of the probability of being most effective, in just over half of all simulations (51%), once daily combined vitamin D or vitamin D analogues and potent corticosteroid emerges as the most effective topical. In a further 28% of simulations concurrent vitamin D or vitamin D analogues and potent corticosteroid emerges as the most effective topical strategy. This means that in nearly 75% of all simulations, a combination of vitamin D or vitamin D analogues and potent corticosteroid, applied separately in two products or applied together in one product, was the most effective topical among all topical therapies evaluated. Once daily potent corticosteroid was most effective in just 12% of simulations. These results are markedly different from the results based on the investigator assessed outcome (IAGI/PGA) where very potent corticosteroids had a 75% probability of being most effective. This is likely due to differences in the availability of data between investigator assessed and patient assessed outcomes.

As for the investigator assessed outcome (IAGI/PGA), the network meta-analysis provides an indication of the overall rank of topical treatments in terms of their relative effectiveness as assessed by the patient him/herself. The results in terms of rank appear to differ between the patient assessed and investigator assessed outcomes, potentially for two reasons. First, there was less PAGI data available to inform estimates of effect than IAGI/PGA data. This limitation could result in seemingly inconsistent measures of effect between the two outcomes. Secondly, it is possible that patient assessment of 'clear or nearly clear' differs from investigator assessment, and this could give rise to slightly different results.

As in the investigator assessed results, once and twice daily vehicle/placebo are consistently the least effective topical therapies, never ranking better than between least and 4th least effective.

As for active treatments, the results indicate that once daily application of vitamin D or vitamin D analogue and of dithranol were consistently among the least effective topical interventions.

The results also show that twice daily application of vitamin D or vitamin D analogues, potent corticosteroid and very potent corticosteroid perform moderately well overall, consistently ranking between 4th and 6th most effective. They are neither the most effective nor the least effective.

As indicated by the high relative risks for once daily potent corticosteroid and combined or concurrent vitamin D or vitamin D analogues and potent corticosteroid, these were consistently ranked among the most effective (i.e. most to 3rd most effective).

At odds with the results of the investigator assessed evidence is the result showing once daily potent corticosteroid to be more effective than both twice daily potent and very potent corticosteroid. This difference is more than likely caused by a difference in the study data available as opposed to a difference in assessment of efficacy or actual efficacy.

The residual deviance of the base case model was 32.79, with the number of unconstrained data points being 33. The closeness of these values indicates a good model fit.

K.5 Sensitivity Analyses

In a sensitivity analysis we explored the impact of a slightly different protocol on the results of the base case. In the sensitivity analysis, we included 2 studies which were excluded from the review of direct evidence on the basis that they reported the wrong comparison. One study{Thawornchaisit, 2007 THAWORNCHAISIT2007 /id} compared twice daily potent corticosteroid with twice daily crude coal tar. Another study{Menter, 2009 MENTER2009A /id} compared once daily combined product containing vitamin D analogue and potent corticosteroid with twice daily very potent corticosteroid.

In the sensitivity analysis, we also included data from a study conducted in children{Oranje, 1997 ORANJE1997 /id} which compared twice daily vehicle/placebo with twice daily vitamin D or vitamin D analogues. These data were kept separate from the largely adult data in the pairwise comparison.

Finally, we also included a further comparator in the sensitivity analysis – twice daily combined vitamin D or vitamin D analogues and potent corticosteroid. It was excluded from the base case and the review of direct evidence because it is currently unlicensed at a twice daily application frequency. Although this did not add any new studies to the existing networks of evidence, it did mean that we would include an additional trial arm of several included studies.

The dashed lines in Figure 1 and Figure 4 present the network diagrams when these studies and comparators were included, for the clear/nearly clear outcomes as assessed by IAGI or PGA and PAGI, respectively.

Table 4 presents the relative risk of each intervention compared to twice daily vehicle/placebo for the outcome of clear/nearly clear on the investigator assessed outcome (IAGI/PGA). It also gives a probability that the intervention is the most effective overall in this sensitivity analysis as well as in the base case. This provides an easy way of comparing the results between the base case and the sensitivity analysis.

Table 4: Relative risks of clear/nearly clear on IAGI/PGA for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower Credible Interval	Upper Credible Interval	Probability most effective in SA	Probability most effective in base case
Combined vitamin D and potent corticosteroid BD	5.914	4.879	6.546	47.3%	NA
Very potent corticosteroid BD	5.711	4.465	6.537	28.1%	48.5%
Combined vitamin D and potent corticosteroid OD	5.192	3.732	6.207	3.0%	12.8%
Very potent corticosteroid OD	4.992	1.644	6.796	18.7%	25.6%
Potent corticosteroid BD	4.708	3.528	5.707	0.2%	1.8%
Concurrent vitamin D and potent corticosteroid	4.673	2.713	6.121	2.6%	7.7%
Vitamin D or vitamin D analogue BD	3.837	2.864	4.75	0.0%	0.0%
Potent corticosteroid OD	3.533	1.65	5.419	0.0%	0.1%
Vitamin D or vitamin D analogue OD	3.187	1.687	4.89	0.0%	0.0%
Dithranol OD	3.001	1.59	4.642	0.0%	0.1%
Coal Tar BD	2.886	1.332	4.8	0.0%	3.1%
Tazarotene OD	2.039	0.5199	4.818	0.0%	0.1%
Coal Tar OD	0.8603	0.1121	3.646	0.0%	0.1%
Placebo OD	0.7507	0.2519	1.851	0.0%	0.0%

Results of the sensitivity analysis indicate two things. First, it demonstrates that the risk ratios from the base case for most topical therapies compared to twice daily vehicle/placebo are insensitive to the additional data. In other words, the median point estimates and their 95% credible intervals have changed very little, and therefore we can be confident in the treatment effect estimates generated in the base case.

Secondly, the results of the sensitivity analysis demonstrate how effective twice daily combined vitamin D analogue and potent corticosteroid is compared to alternatives. Indeed, when it is included as a relevant comparator, it emerges as the most effective strategy in nearly 50% of simulations. Interestingly, the pairwise odds ratios from the sensitivity analysis (Figure 7) indicate that based on direct evidence from one study{Guenther, 2002 GUENTHER2002 /id} alone, twice daily combined vitamin D analogue and potent corticosteroid is more effective than once daily (OR 1.61 (1.03 to 2.5). However, when all direct and indirect evidence is combined, this difference does not reach statistical significance (OR 1.76 (0.65 to 4.91)).

Figure 7: Odds ratios for clear/nearly clear as measured by IAGI or PGA, results of sensitivity analysis wherein all data and twice daily combined vitamin D analogue and potent corticosteroid are included

Placebo OD		**4.82** **3.12 to 7.44**		**5** **3.12 to 8.01**		**17.92** **6.54 to 49.14**		**2.98** **1.45 to 6.12**	**12.11** **7.56 to 19.39**					
1.386 0.466 to 4.45	Placebo BD		**7.73** **5.81 to 10.29**		**12.47** **6.81 to 22.85**		**14.67** **8.84 to 24.34**		**6.73** **3.92 to 11.53**	**31.47** **20.09 to 49.3**				
6.85 **3.371 to 15.44**	**4.93** **1.898 to 13.2**	Vitamin D OD	**1.69** **1.08 to 2.63**	**2.00** **1.52 to 2.63**					**4.44** **3.63 to 5.43**		**2.95** **1.89 to 4.61**			
9.816 **3.412 to 30.3**	**7.087** **4.1 to 12.1**	1.44 0.563 to 3.499	Vitamin D BD		**1.54** **1.28 to 1.82**				**1.76** **1.37 to 2.26**	**3.87** **3.17 to 4.71**	**1.98** **1.41 to 2.76**	**0.13** **0.03 to 0.56**	0.78 0.43 to 1.39	**0.51** **0.39 to 0.67**
8.328 **3.83 to 18.86**	**5.982** **1.843 to 19**	1.217 0.514 to 2.714	0.8465 0.272 to 2.593	Potent corticosteroid OD					**2.15** **1.69 to 2.73**					
16.38 **5.036 to 57.63**	**11.75** **5.966 to 23.8**	2.396 0.823 to 6.751	1.658 0.935 to 3.053	1.97 0.57 to 6.906	Potent corticosteroid BD					**2.48** **1.97 to 3.11**			**0.10** **0.03 to 0.34**	
19.49 **3.759 to 108.4**	**14.07** **1.834 to 107**	2.839 0.453 to 17.4	1.986 0.27 to 14.68	2.351 0.37 to 15.29	1.194 0.148 to 9.239	Very potent corticosteroid OD								
33.38 **9.587 to 131.3**	**23.92** **10.15 to 62.2**	**4.882** **1.517 to 16.06**	**3.378** **1.314 to 9.589**	**4.018** **1.12 to 15.77**	2.037 0.709 to 6.253	1.705 0.217 to 14.68	Very potent corticosteroid BD		0.71 0.29 to 1.71					
3.417 **1.059 to 11.97**	2.451 0.483 to 12.6	0.4988 0.119 to 2.058	0.3451 0.07 to 1.747	0.4093 0.1 to 1.787	0.2086 0.038 to 1.128	0.1764 0.022 to 1.385	**0.1022** **0.02 to 0.568**	Retinoid OD						
22.36 **10.3 to 52.44**	**16.1** **6.684 to 39.2**	**3.275** **1.696 to 6.095**	2.271 0.974 to 5.388	**2.688** **1.17 to 6.4**	1.368 0.506 to 3.702	1.144 0.18 to 7.371	0.6711 0.22 to 1.874	**6.573** **1.535 to 28.06**	Combined vitamin D and Potent corticosteroid OD	**1.61** **1.03 to 2.5**				
39.71 **12.29 to 142.5**	**28.72** **13.07 to 63.1**	**5.797** **1.938 to 17.04**	**4.038** **1.992 to 8.386**	**4.78** **1.38 to 17.33**	**2.431** **1.111 to 5.336**	2.04 0.258 to 16.35	1.198 0.37 to 3.619	**11.7** **2.11 to 65.85**	1.776 0.65 to 4.913	Combined vitamin D and Potent corticosteroid BD				
15.96 **4.43 to 62.35**	**11.5** **3.752 to 35.5**	2.345 0.729 to 7.182	1.62 0.601 to 4.562	1.921 0.51 to 7.53	0.9797 0.301 to 3.149	0.8167 0.1 to 7.134	0.4787 0.12 to 1.813	4.662 0.805 to 28.08	0.713 0.223 to 2.292	0.4007 0.121 to 1.369	Concurrent vitamin D and Potent			
1.156 0.114 to 11.28	0.8413 0.098 to 6.37	0.1673 0.017 to 1.448	**0.1187** **0.015 to 0.839**	0.1391 0.01 to 1.351	**0.071** **0.008 to 0.55**	**0.05912** **0.003 to 0.992**	**0.03477** **0 to 0.302**	0.3357 0.025 to 4.347	**0.05186** **0.005 to 0.438**	**0.02921** **0.003 to 0.234**	**0.0725** **0.007 to 0.656**	Coal Tar OD		
5.808 **1.387 to 25.44**	**4.15** **1.407 to 12.4**	0.8418 0.219 to 3.09	0.5866 0.225 to 1.582	0.6925 0.16 to 3.033	**0.353** **0.124 to 0.996**	0.2942 0.033 to 2.731	**0.1733** **0.04 to 0.659**	1.695 0.266 to 11.01	**0.2577** **0.072 to 0.93**	**0.145** **0.044 to 0.473**	0.3611 0.087 to 1.446	4.957 0.543 to 49.78	Coal Tar BD	
6.184 **1.677 to 24.37**	**4.435** **1.758 to 11.3**	0.9015 0.268 to 2.934	0.6272 0.296 to 1.354	0.7438 0.19 to 2.897	**0.3771** **0.144 to 0.989**	0.318 0.037 to 2.674	**0.185** **0.05 to 0.631**	1.81 0.3 to 10.96	**0.2757** **0.087 to 0.867**	**0.1541** **0.055 to 0.442**	0.3857 0.106 to 1.353	5.302 0.648 to 49.11	**1.068** **0.309 to 3.703**	Dithranol 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.

Table 5 presents the relative risk of achieving clearance or near clearance as assessed by the patient (PAGI) for each intervention compared to twice daily vehicle/placebo. It also gives a probability that the intervention is the most effective overall in this sensitivity analysis as well as in the base case. This provides an easy way of comparing the results between the base case and the sensitivity analysis.

Table 5: Relative risks of clear/nearly clear with PAGI for all interventions compared to twice daily vehicle/placebo

Intervention	Median RR	Lower CrI	Upper CrI	Probability most effective in SA	Probability most effective in base case
Combined vitamin D analogue and potent corticosteroid BD	4.542	3.395	5.346	54.30%	NA
Combined vitamin D analogue and potent corticosteroid OD	4.296	2.881	5.291	24.10%	51.54%
Potent corticosteroid OD	3.936	2.469	5.12	8.20%	12.24%
Concurrent vitamin D analogue and potent corticosteroid	3.673	1.667	5.282	11.30%	27.64%
Vitamin D or vitamin D analogue BD	2.817	1.857	3.833	0.00%	1.57%
Potent corticosteroid BD	2.734	1.562	4.079	0.10%	2.80%
Very potent corticosteroid BD	2.59	1.096	4.392	1.90%	3.69%
Vitamin D or vitamin D analogue OD	2.225	1.049	3.759	0.00%	0.01%
Dithranol OD	1.705	0.6535	3.448	0.00%	0.50%
Placebo OD	1.496	0.5293	3.222	0.00%	0.01%

As in the case of the IAGI and PGA outcomes, the results of the analysis demonstrate that the majority of the base case results are robust to changes in the data. The one noteworthy exception is twice daily vitamin D or vitamin D analogue. The base case showed the relative risk for twice daily vitamin D or vitamin D analogue compared to twice daily vehicle/placebo was 3.56 (2.16 to 4.92). In the sensitivity analysis, twice daily vitamin D or vitamin D analogue appears to be less effective than in the base case (but still more effective than vehicle/placebo) with a relative risk of 2.82 (1.86 to 3.83).

The effectiveness of twice daily combined vitamin D analogue and potent corticosteroid is also demonstrated for this patient-reported outcome. Again, it has a greater than 50% probability of being the most effective topical therapy. But again, the pairwise odds ratios of direct evidence (Figure 8) indicate that there is a non-significant difference between once daily and twice daily application of the combined product (OR 1.22 (0.47 to 3.24)).

Figure 8: Odds ratios for clear/nearly clear as measured by PAGI, results of sensitivity analysis wherein all data and twice daily combined vitamin D analogue and potent corticosteroid are included

Placebo OD		**2.39** **1.56 to 3.67**		**7.86** **4.48 to 13.79**			**8.31** **5.51 to 12.54**			
0.738 0.164 to 3.221	Placebo BD		**4.36** **3.21 to 5.92**		**11.19** **6.27 to 19.95**	**3.73** **2.27 to 6.12**	**13.05** **7.67 to 22.19**	**17.89** **12.10 to 26.46**		
1.854 0.645 to 5.323	2.53 0.756 to 8.51	Vitamin D OD	**1.85** **1.16 to 2.86**	**2.08** **1.59 to 2.70**			**4.47** **3.64 to 5.48**		**2.87** **1.83 to 4.50**	
3.312 0.811 to 12.98	**4.478** **2.186 to 9.18**	1.776 0.6 to 5.237	Vitamin D BD		**1.69** **1.41 to 2.04**		**1.77** **1.16 to 2.71**	**3.8** **2.94 to 4.90**	**1.56** **1.02 to 2.39**	**0.44** **0.32 to 0.60**
4.548 **1.126 to 18.57**	**6.156** **1.162 to 33.7**	2.443 0.662 to 9.249	1.378 0.287 to 6.902	Potent corticosteroid OD			**2.19** **1.69 to 2.83**			
4.143 0.918 to 18.63	**5.641** **2.404 to 13.4**	2.221 0.646 to 7.847	1.257 0.642 to 2.527	0.9092 0.16 to 4.948	Potent corticosteroid BD			**1.88** **1.50 to 2.36**		
2.71 0.369 to 20.02	**3.667** **1.009 to 14.3**	1.451 0.241 to 8.818	0.8235 0.189 to 3.796	0.5948 0.07 to 5.004	0.6513 0.138 to 3.194	Very potent corticosteroid BD				
7.556 **2.638 to 21.73**	**10.3** **3.266 to 32.1**	**4.086** **1.851 to 8.978**	2.298 0.818 to 6.509	1.667 0.45 to 6.092	1.826 0.556 to 5.923	2.798 0.471 to 16.16	Combined vitamin D and Potent corticosteroid OD	1.24 0.8 to 1.93		
10.47 **2.294 to 47.06**	**14.27** **5.793 to 34.4**	**5.638** **1.655 to 19.2**	**3.178** **1.467 to 6.96**	2.295 0.42 to 12.3	**2.527** **1.063 to 6.02**	3.868 0.769 to 18.74	1.382 0.44 to 4.444	Combined vitamin D and Potent corticosteroid BD		
5.317 0.922 to 29.03	**7.257** **1.532 to 33.8**	2.855 0.686 to 11.75	1.608 0.398 to 6.475	1.166 0.17 to 7.453	1.278 0.269 to 5.946	1.967 0.247 to 14.92	0.7006 0.15 to 3.155	0.5052 0.105 to 2.418	Concurrent vitamin D and Potent corticosteroid	
1.509 0.261 to 8.623	2.043 0.557 to 7.4	0.8099 0.177 to 3.731	0.4557 0.156 to 1.323	0.3297 0.05 to 2.211	0.3638 0.101 to 1.279	0.554 0.085 to 3.507	**0.1983** **0.04 to 0.88**	**0.1433** **0.038 to 0.535**	0.2834 0.049 to 1.638	Dithranol 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.

K.6 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 mild to moderate psoriasis 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 38 studies, including up to 11,931 patients randomised to 14 different interventions. These studies formed 2 networks of evidence, which were differentiated by outcome. The first network is comprised of evidence on the effectiveness of topical therapies in achieving a physician or investigator assessed outcome of response (clear/nearly clear); the second network is comprised of evidence on the effectiveness of a subset of the same topical therapies in terms of a patient assessed outcome of response (clear/nearly clear). Fewer trials reported data for the patient assessed outcome than the investigator assessed outcome. The findings from the NMA fed into the original economic analysis of topical therapy sequences (see Appendix M), and helped to facilitate GDG decision-making about the optimal treatments for patients with mild to moderate plaque psoriasis of the trunk and limbs.

Results of the first network, in which outcomes were based on investigator/physician assessment, showed that all topicals with active agents (non-vehicle cream or ointment) were more effective than placebo/vehicle. There was a non-significant trend towards twice daily application of a given topical to be more effective than once daily application. Very potent corticosteroids were found to be among the most effective agents in terms of induction of clearance or near clearance, and once or twice daily application was shown to be the most effective intervention in nearly 75% of simulations. The next most effective interventions involved a combination of potent corticosteroid and vitamin D analogue, either applied once daily in a single two-compound formulation product or applied separately, one in the morning and the other in the evening. Interventions such as potent corticosteroids and vitamin D analogues, coal tar and dithranol were all between 3 and 5 times more likely to induce clearance than placebo, but there were only small and non-significant differences between them.

In a sensitivity analysis of the first network, the protocol was broadened to include additional trial evidence and comparators. Twice daily application of two-compound formulation product (combined potent corticosteroid and vitamin D analogue) was excluded from the base case because it is not licensed at this high dose, but it was included in the sensitivity analysis. Results showed that the conclusions from the base case were somewhat sensitive to the additional data and comparators. The overall ranking of strategies was largely consistent; however twice daily coal tar was less effective than in the base case. The additional comparator, twice daily two-compound formulation product, was found to be the most effective intervention, surpassing very potent corticosteroids. When compared to once daily application, the twice daily two-compound formulation product trended toward being more effective, but this trend failed to reach statistical significance.

Results of the second network, in which outcomes were based on patient assessment, were broadly similar to the results from the investigator/physician assessed analysis. The effectiveness of very potent corticosteroid was markedly less when assessed by patients, but it is unclear what may be driving this finding. Combined and concurrent potent corticosteroid and vitamin D analogue were the best topicals, followed by potent corticosteroids and vitamin D analogues. In this analysis, once daily potent corticosteroid performed slightly better than twice daily, but twice daily vitamin D or vitamin D analogue was more effective than once daily. Again, when the protocol was expanded and

twice daily two-compound formulation product was included as a comparator, it was shown to be most effective, but not significantly more effective than once daily application.

The NMA was undertaken to synthesise estimates of efficacy for different topical therapies under consideration for the treatment of mild to moderate psoriasis. 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 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.

K.7 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

for (k in 1:NT) {                                                 # Ranking and prob{treatment k is best}
            rk[k]<-NT+1-rank(rr[],k)
best[k]<-equals(NT+1-rank(rr[],k),1)}
for (c in 1:(NT-1))                                               # pairwise ORs and RRs
        {  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=35,NT=14)

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[]

1 26 13 28 NA 1 NA 1 NA NA 2 3 NA NA NA 2

0 84 37 84 NA 1 NA 1 NA NA 2 3 NA NA NA 2

0 40 9 79 14 83 44 162 NA NA 2 3 5 10 NA 4

16 157 107 480 176 476 276 490 NA NA 2 3 5 10 NA 4

5 91 33 184 73 183 NA 1 NA NA 2 3 10 NA NA 3

7 45 18 50 NA 1 NA 1 NA NA 2 5 NA NA NA 2

7 44 27 46 NA 1 NA 1 NA NA 2 5 NA NA NA 2

5 33 144 189 NA 1 NA 1 NA NA 2 7 NA NA NA 2

7 229 24 439 NA 1 NA 1 NA NA 2 9 NA NA NA 2

2 214 26 421 NA 1 NA 1 NA NA 2 9 NA NA NA 2

9 29 21 29 NA 1 NA 1 NA NA 1 4 NA NA NA 2

13 32 24 32 NA 1 NA 1 NA NA 1 4 NA NA NA 2

23 123 87 124 NA 1 NA 1 NA NA 1 4 NA NA NA 2

11 62 46 62 NA 1 NA 1 NA NA 1 4 NA NA NA 2

8 107 103 308 174 312 NA 1 NA NA 1 4 6 NA NA 3

19 206 115 227 95 150 NA 1 NA NA 1 4 10 NA NA 3

4 37 15 39 NA 1 NA 1 NA NA 1 6 NA NA NA 2

1 83 12 78 NA 1 NA 1 NA NA 1 6 NA NA NA 2

0 29 84 162 NA 1 NA 1 NA NA 1 8 NA NA NA 2

27 125 85 120 NA 1 NA 1 NA NA 1 8 NA NA NA 2

1 20 10 61 NA 1 NA 1 NA NA 1 8 NA NA NA 2

2 60 47 60 NA 1 NA 1 NA NA 1 8 NA NA NA 2

49 172 69 172 73 172 NA 1 NA NA 3 4 11 NA NA 3

43 252 143 249 NA 1 NA 1 NA NA 3 10 NA NA NA 2

67 128 81 130 NA 1 NA 1 NA NA 4 6 NA NA NA 2

119 205 116 207 NA 1 NA 1 NA NA 4 6 NA NA NA 2

142 365 169 363 NA 1 NA 1 NA NA 4 6 NA NA NA 2

```
22 49 27 39 NA 1 NA 1 NA NA 4 11 NA NA NA 2

13 27 3 27 NA 1 NA 1 NA NA 4 12 NA NA NA 2

6 28 14 27 NA 1 NA 1 NA NA 4 13 NA NA NA 2

47 65 28 57 NA 1 NA 1 NA NA 4 13 NA NA NA 2

23 60 24 54 NA 1 NA 1 NA NA 4 14 NA NA NA 2

92 153 67 131 NA 1 NA 1 NA NA 4 14 NA NA NA 2

180 231 116 227 NA 1 NA 1 NA NA 4 14 NA NA NA 2

6 89 4 77 NA 1 NA 1 NA NA 4 14 NA NA NA 2

END


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

sd=.2,

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

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

),.Dim=c(35 , 14)))
```

K.8 References