NCGC National Clinical Guideline Centre

Royal College of Nursing

RCS ADVANCING SURGICAL STANDARDS

RCGP Royal College of General Practitioners

NCGC National Clinical Guideline Centre

Royal College of Nursing

RCS ADVANCING SURGICAL STANDARDS

RCGP Royal College of General Practitioners

NCGC National Clinical Guideline Centre

Royal College of Nursing

RCS ADVANCING SURGICAL STANDARDS

RC GP Royal College of General Practitioners

NHS Evidence accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

NCGC National Clinical Guideline Centre

Psoriasis Guideline

Appendices J - U

Psoriasis Guideline

Appendices J-U

October 2012

Commissioned by the National Institute for Health and Clinical Excellence

Royal College of Physicians
Setting higher medical standards

Royal College of Nursing

RCS
ADVANCING SURGICAL STANDARDS

RCGP Royal College of General Practitioners

Psoriasis

Contents

Appendix J: Forest plots

J.1 Diagnostic tools for psoriatic arthritis

Diagnostic tools for Psoriatic Arthritis

Figure 1: ToPAS vs clinical diagnosis by rheumatologist

Study	TP	FP	FN	TN	Sensitivity	Specificity
Gladman 2009	146	13	18	80	0.89 [0.83, 0.93]	0.86 [0.77, 0.92]

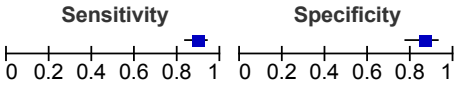
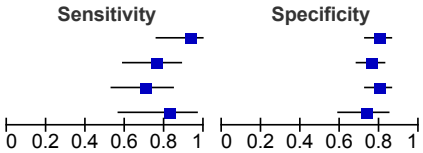


Figure 2: PASE vs clinical diagnosis by rheumatologist

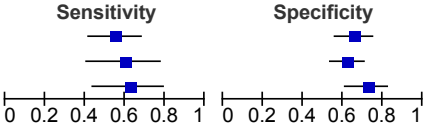
Study	TP	FP	FN	TN	Sensitivity	Specificity
Dominguez 2009 (active)	25	31	2	122	0.93 [0.76, 0.99]	0.80 [0.72, 0.86]
Dominguez 2009 (TH:44)	28	37	9	116	0.76 [0.59, 0.88]	0.76 [0.68, 0.82]
Dominguez 2009 (TH:47)	26	31	11	122	0.70 [0.53, 0.84]	0.80 [0.72, 0.86]
Husini 2007	14	14	3	38	0.82 [0.57, 0.96]	0.73 [0.59, 0.84]



Note: all of the Dominguez data is from the same population

Figure 3: PAQ vs clinical diagnosis by rheumatologist

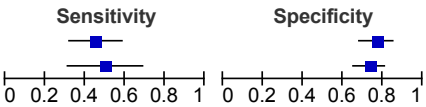
Study	TP	FP	FN	TN	Sensitivity	Specificity
Alenius2002 any arthritis	33	36	27	69	0.55 [0.42, 0.68]	0.66 [0.56, 0.75]
Alenius2002 periph/axial	18	51	12	84	0.60 [0.41, 0.77]	0.62 [0.53, 0.70]
Ibrahim 2009	20	21	12	55	0.63 [0.44, 0.79]	0.72 [0.61, 0.82]



Note: all of the Alenius data is from the same population

Figure 4: mPAQ vs clinical diagnosis by rheumatologist

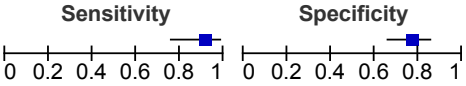
Study	TP	FP	FN	TN	Sensitivity	Specificity
Alenius2002 any arthritis	27	24	33	81	0.45 [0.32, 0.58]	0.77 [0.68, 0.85]
Alenius2002 periph/axial	15	36	15	99	0.50 [0.31, 0.69]	0.73 [0.65, 0.81]



Note: all of the Alenius data is from the same population

Figure 5: PEST vs clinical diagnosis by rheumatologist

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ibrahim 2009	30	19	3	62	0.91 [0.76, 0.98]	0.77 [0.66, 0.85]



J.2 Topicals – trunk and limbs

J.2.1 Vitamin D analogue vs placebo

Figure 6: Investigator's assessment (clear/nearly clear) at 4-10 weeks

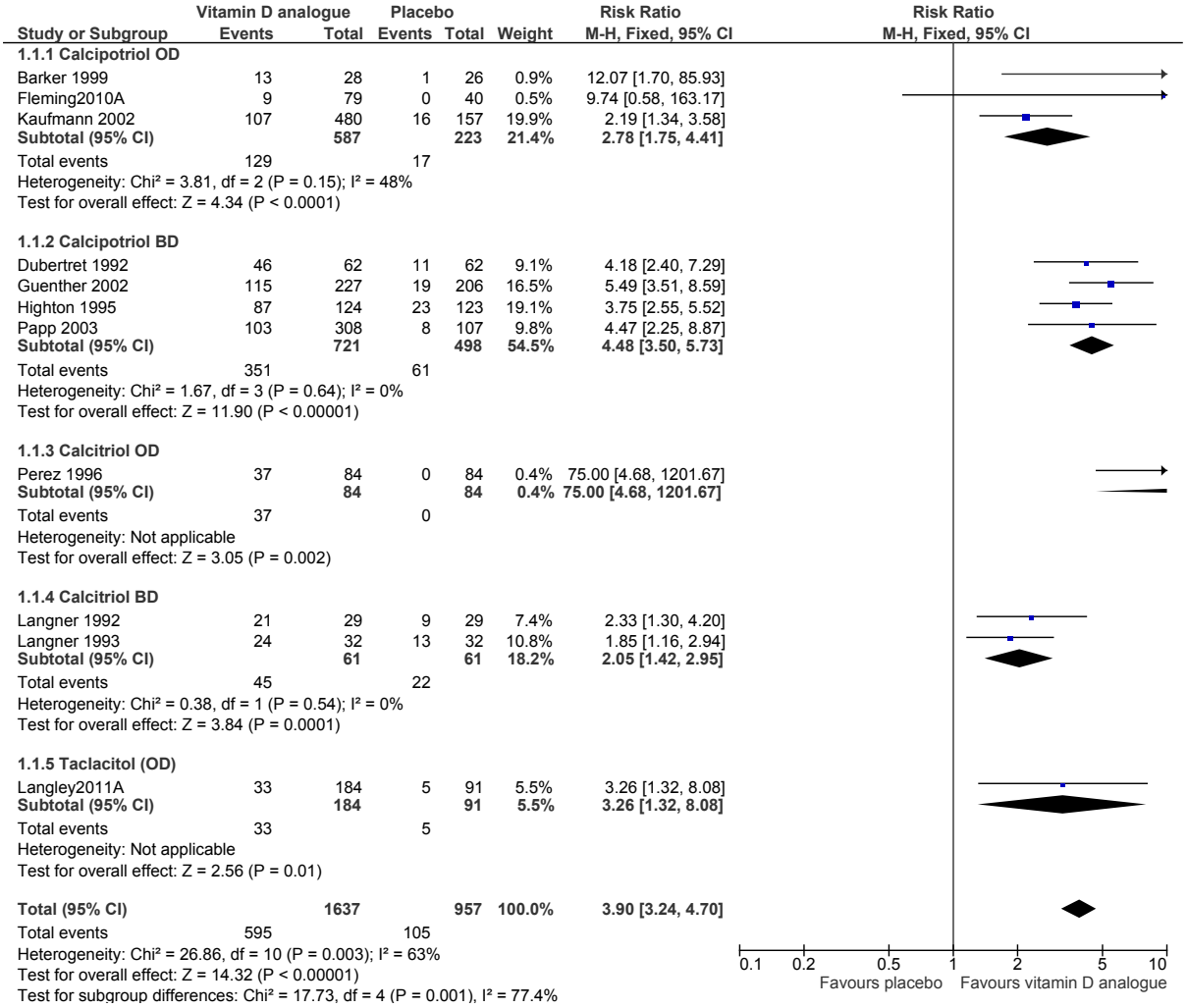


Figure 7: Patient's assessment (clear/nearly clear) at 4-8 weeks

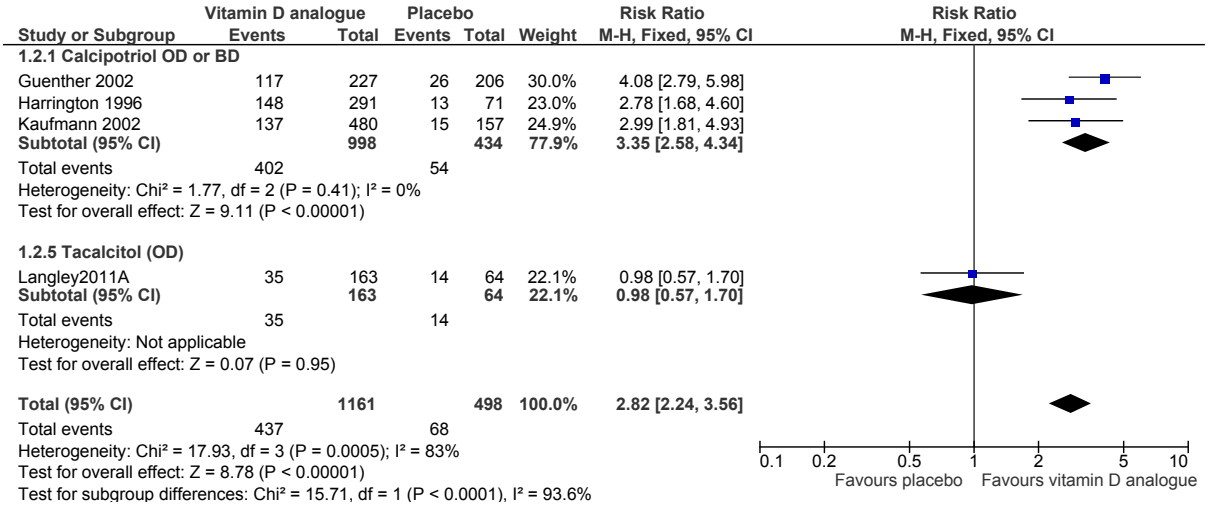


Figure 8: % change in PASI at 4 weeks

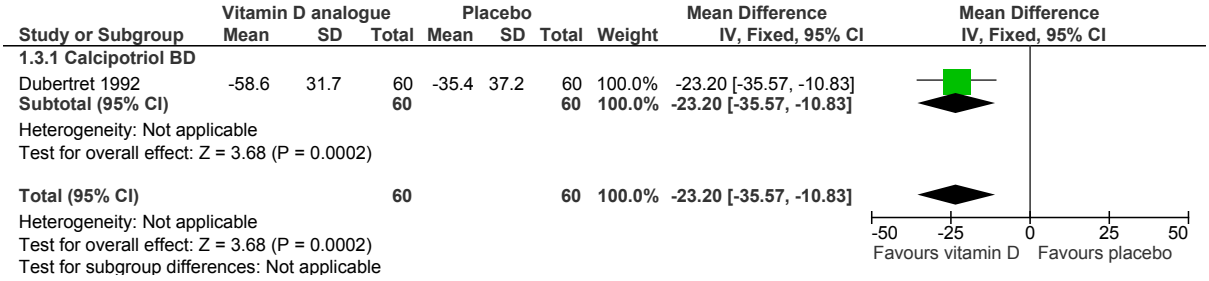


Figure 9: Withdrawals due to adverse events at 4-8 weeks

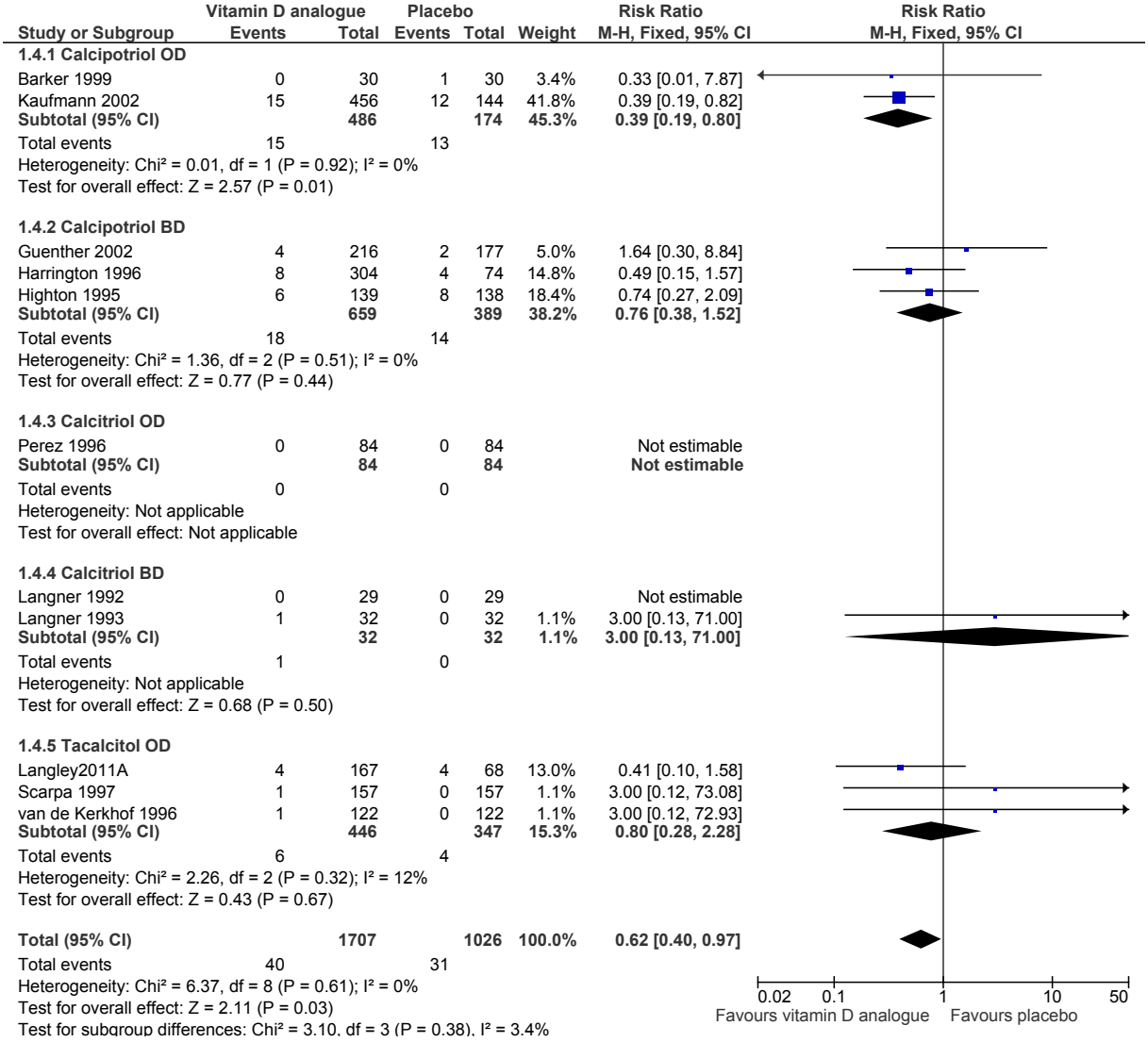


Figure 10: Withdrawals due to lack of efficacy at 4-8 weeks

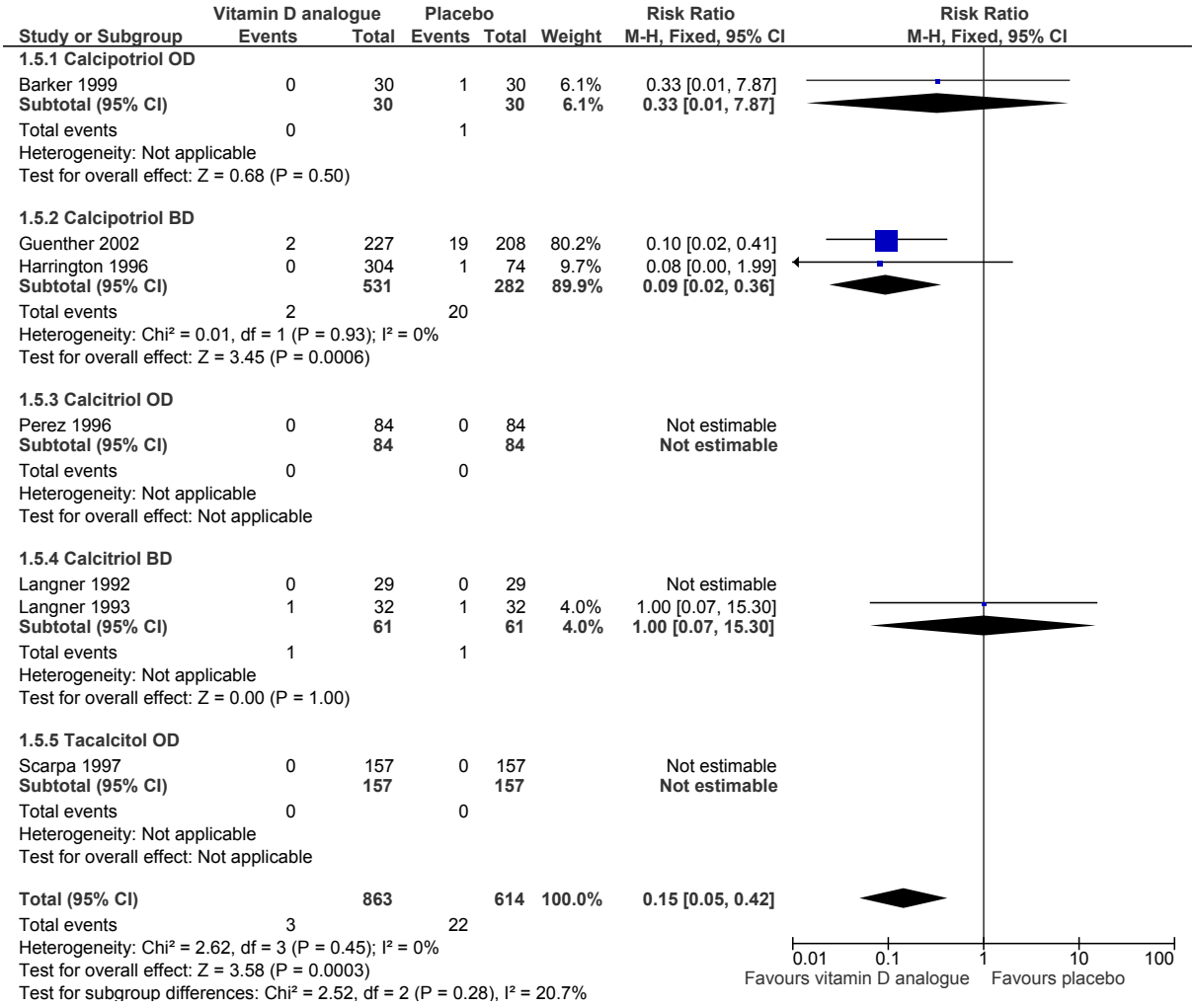


Figure 11: Skin atrophy at 4 weeks

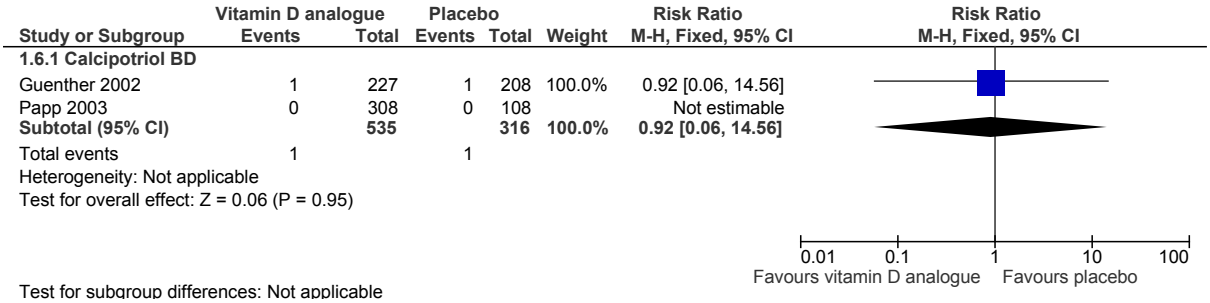
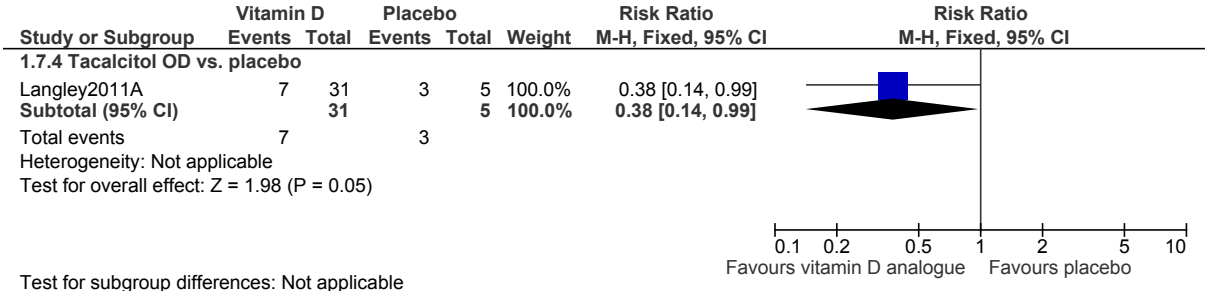


Figure 12: Relapse rate (8 weeks post treatment)



J.2.2 Vitamin D or vitamin D analogue vs placebo (children)

Figure 13: Investigator's assessment (clear/nearly clear) at 8 weeks

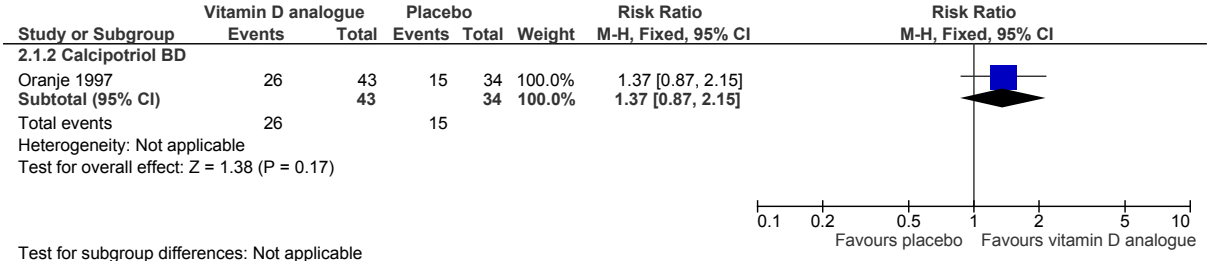


Figure 14: Patient's assessment (clear/nearly clear) at 8 weeks

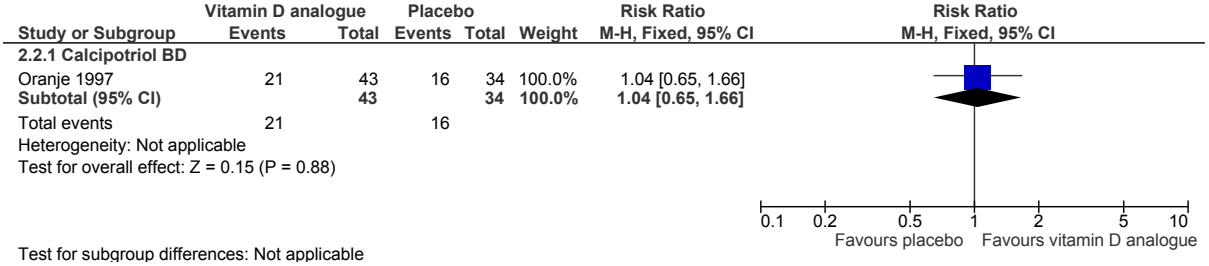
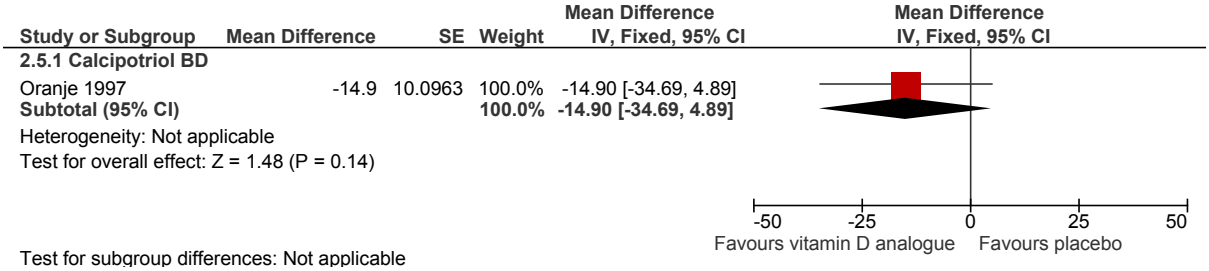


Figure 15: % change in PASI at 8 weeks



J.2.3 Potent corticosteroid vs placebo

Figure 16: Investigator's assessment (clear/nearly clear) at 3-8 weeks

Note: different scale

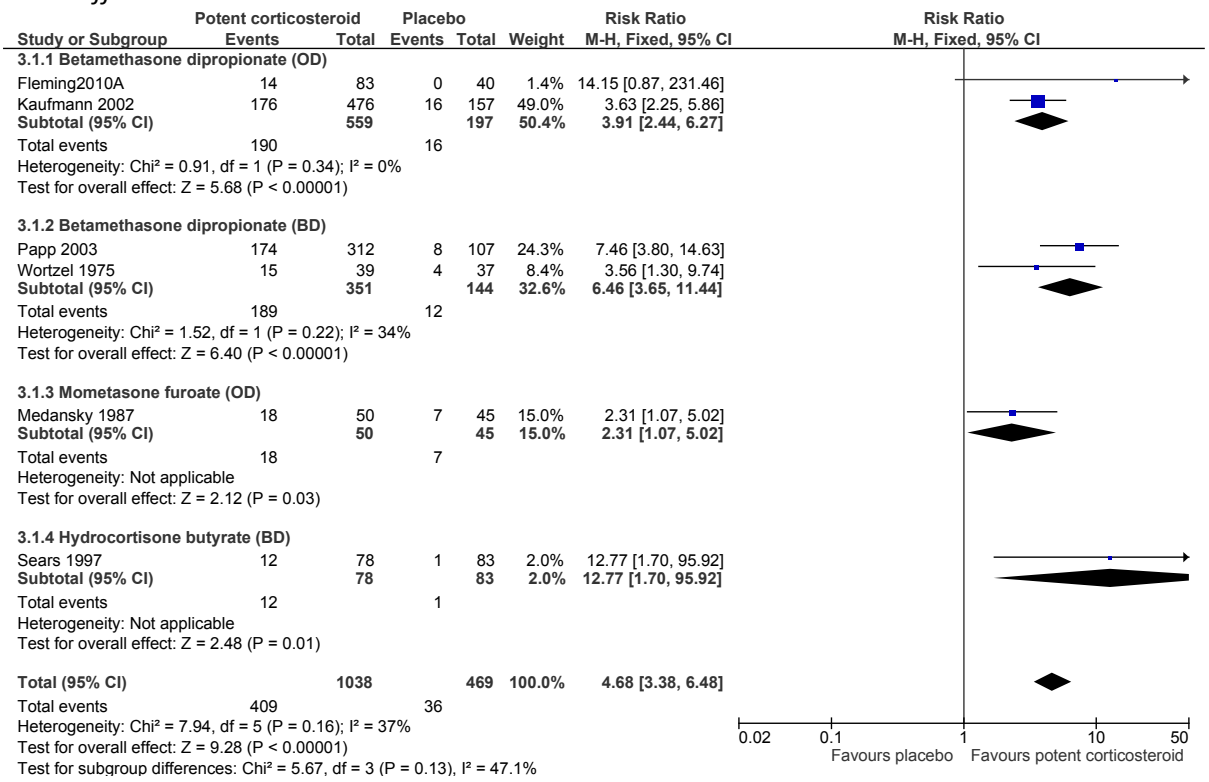


Figure 17: Patient's assessment (clear/nearly clear) at 3-4 weeks

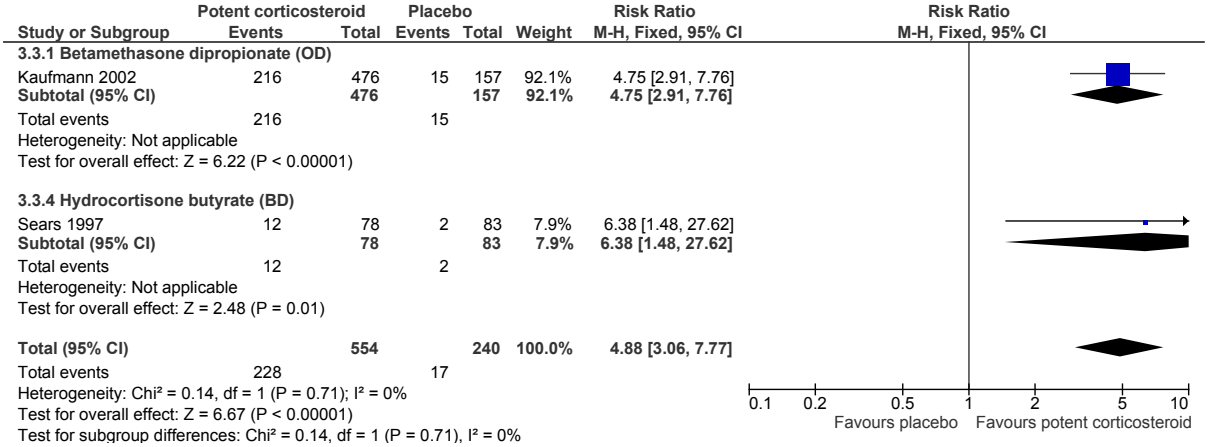


Figure 18: Withdrawals due to adverse events at 3-12 weeks

Note: different scale

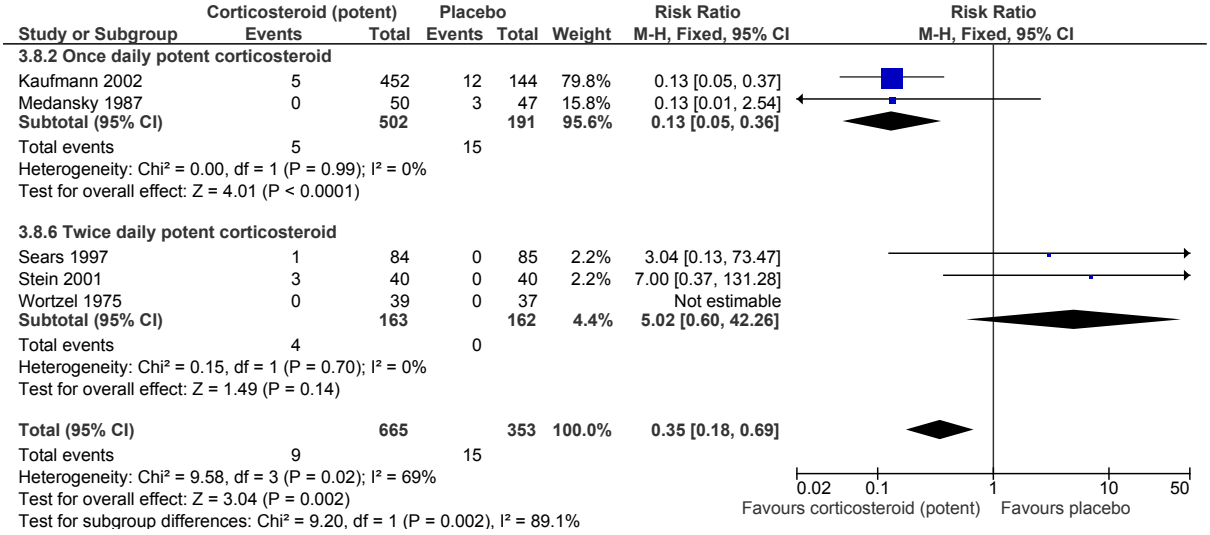
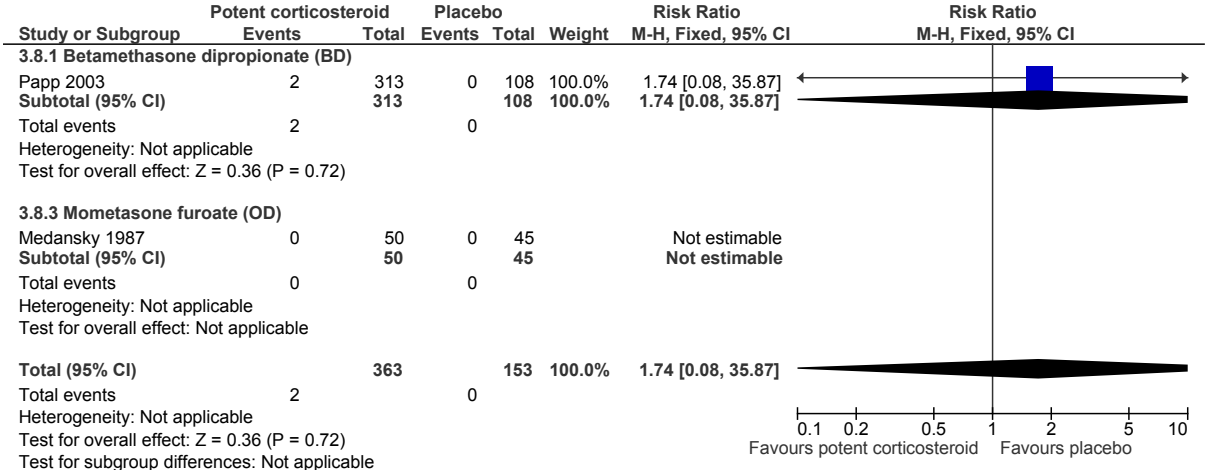


Figure 19: Skin atrophy at 3-4 weeks



J.2.4 Very potent corticosteroid vs placebo

Figure 20: Investigator's assessment (clear/nearly clear) at 2-4 weeks

Note: different scale

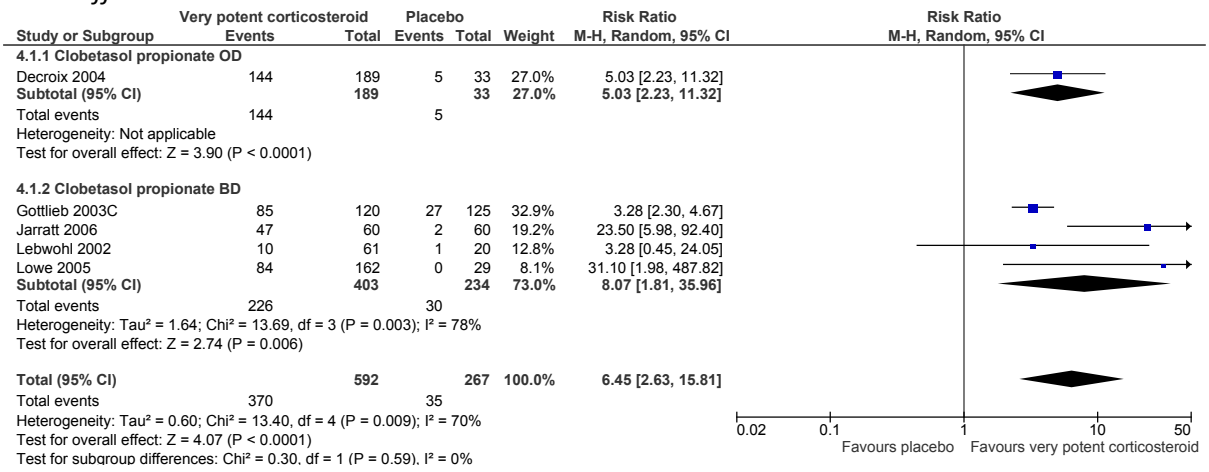


Figure 21: Patient's assessment (clear/nearly clear) at 2 weeks

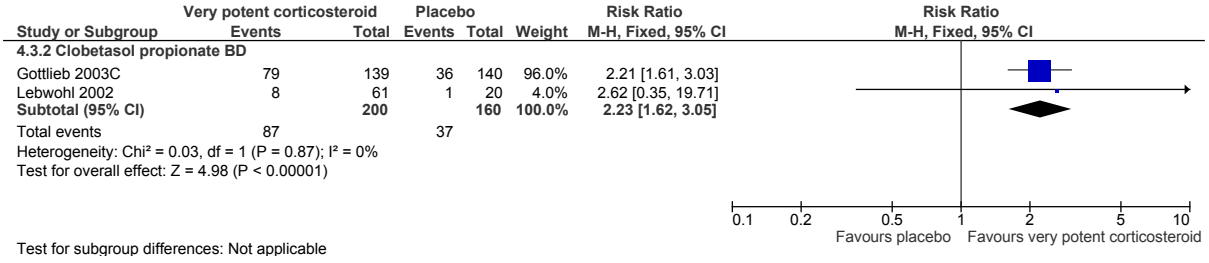


Figure 22: Withdrawals due to adverse events at 2-4 weeks

Note: different scale

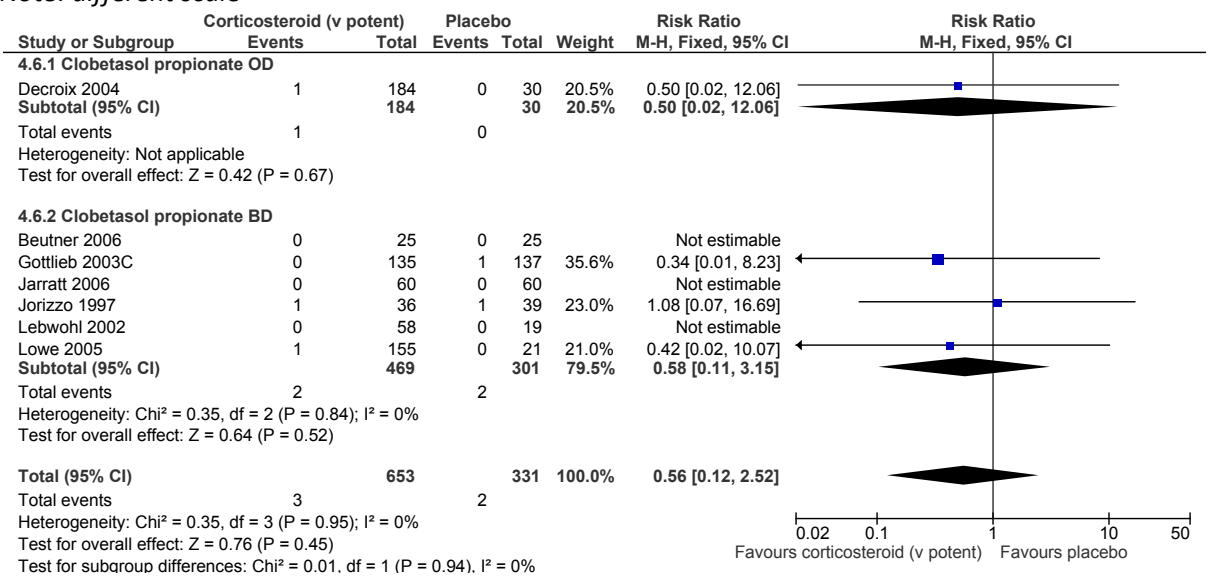


Figure 23: Withdrawals due to lack of efficacy at 4 weeks

Note: different scale

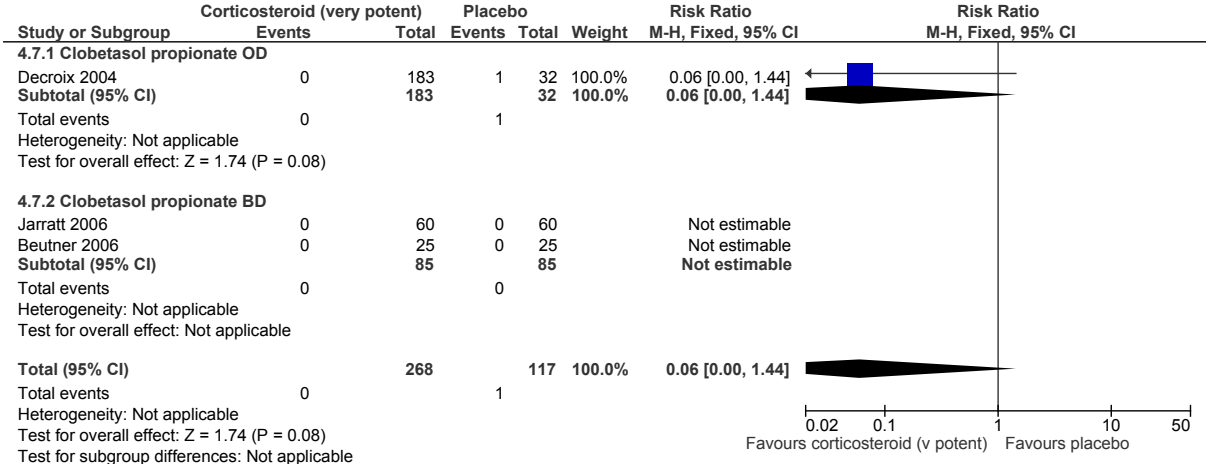
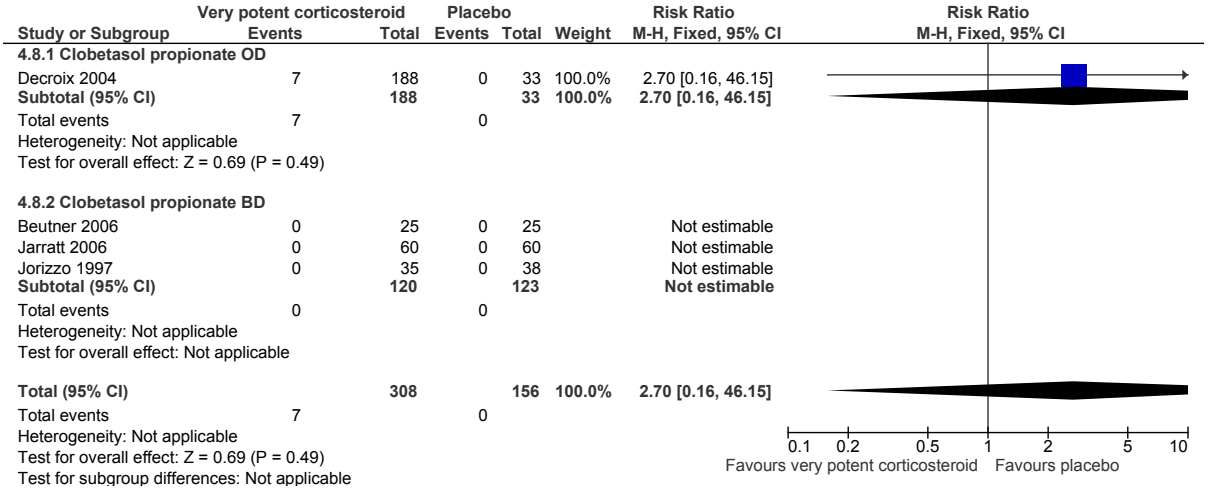


Figure 24: Skin atrophy at 4 weeks

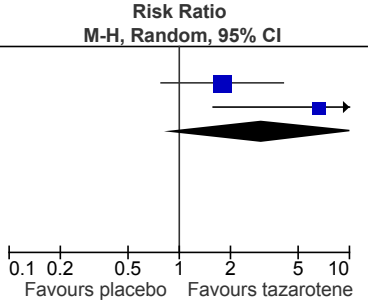


J.2.5 Tazarotene vs placebo

Figure 25: Investigator's assessment (clear/nearly clear) at 12 weeks

Study or Subgroup	Tazarotene Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Tazarotene						
Weinstein 2003 - study A	24	439	7	229	59.7%	1.79 [0.78, 4.09]
Weinstein 2003 - study B	26	421	2	214	40.3%	6.61 [1.58, 27.58]
Subtotal (95% CI)		**860**		**443**	**100.0%**	**3.03 [0.83, 11.07]**
Total events	50		9			

Heterogeneity: Tau² = 0.55; Chi² = 2.56, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 1.67 (P = 0.09)

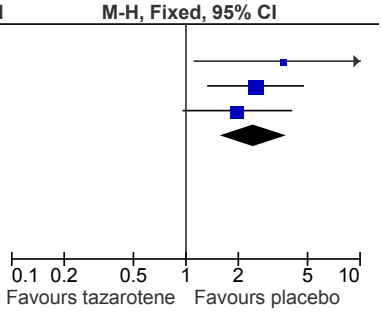


Test for subgroup differences: Not applicable

Figure 26: Withdrawals due to adverse events at 12 weeks

Study or Subgroup	Tazarotene Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Tazarotene						
Weinstein 1996	24	186	3	84	13.5%	3.61 [1.12, 11.67]
Weinstein 2003 - study A	53	439	11	229	47.4%	2.51 [1.34, 4.72]
Weinstein 2003 - study B	35	421	9	214	39.1%	1.98 [0.97, 4.04]
Subtotal (95% CI)		**1046**		**527**	**100.0%**	**2.45 [1.58, 3.80]**
Total events	112		23			

Heterogeneity: Chi² = 0.78, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 4.02 (P < 0.0001)

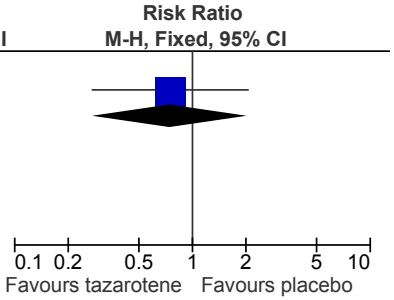


Test for subgroup differences: Not applicable

Figure 27: Withdrawal due to lack of efficacy at 12 weeks

Study or Subgroup	Tazarotene Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 Tazarotene						
Weinstein 1996	9	216	6	108	100.0%	0.75 [0.27, 2.05]
Subtotal (95% CI)		**216**		**108**	**100.0%**	**0.75 [0.27, 2.05]**
Total events	9		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)



Test for subgroup differences: Not applicable

J.2.6 Potent corticosteroid vs placebo (for maintenance of remission)

Figure 28: Investigator's assessment (clear/slight at 24 weeks)

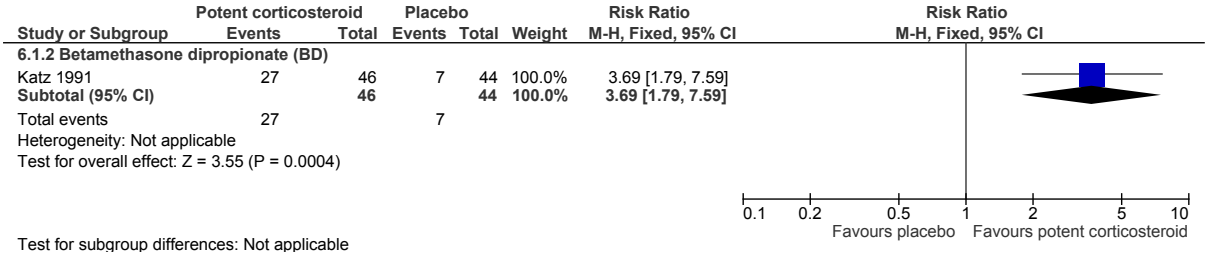
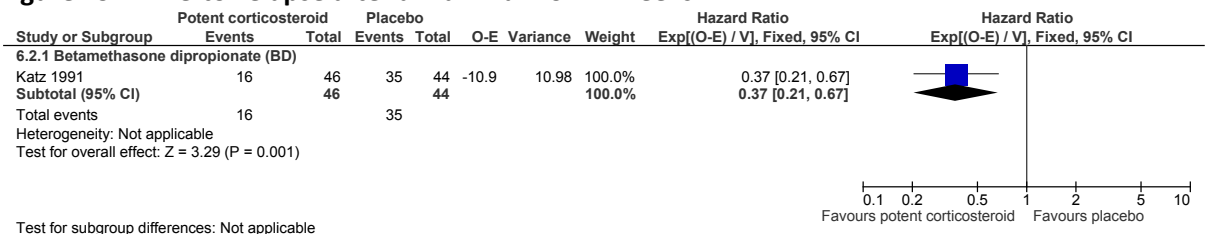


Figure 29: Time-to-relapse after a maximum of 24 weeks



J.2.7 Vitamin D or vitamin D analogue vs potent corticosteroid

Figure 30: Investigator's assessment (clear/nearly clear) at 4-8 weeks

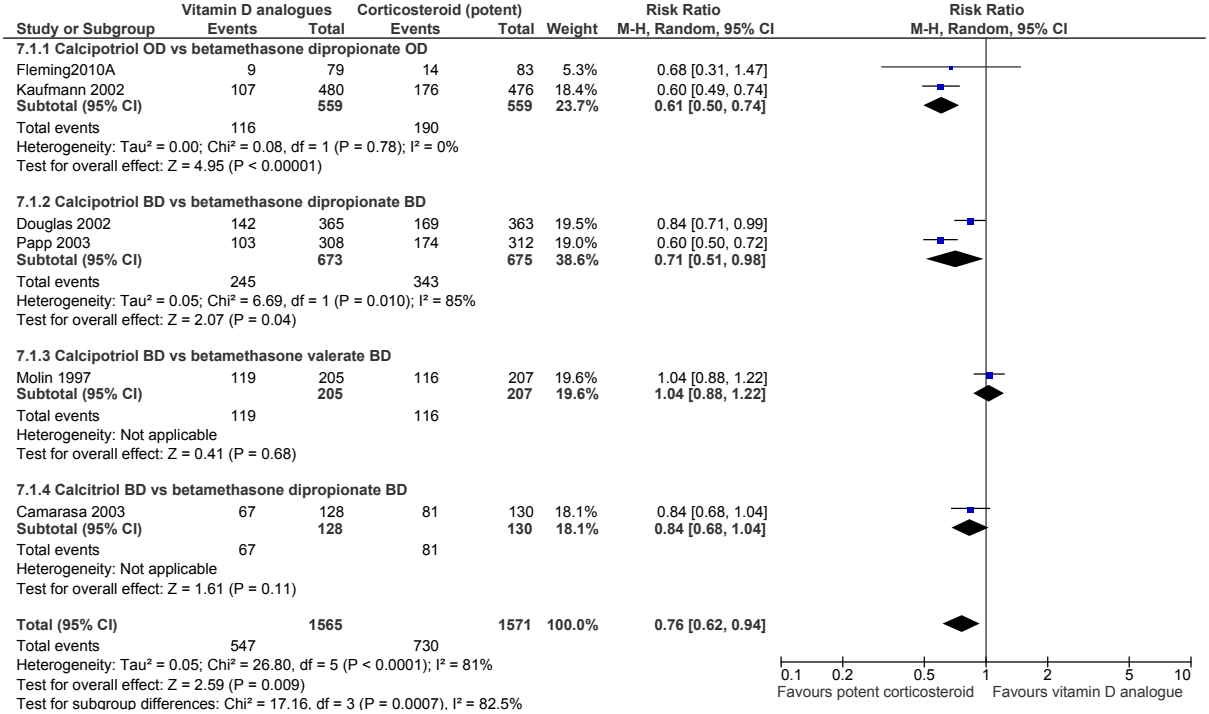


Figure 31: Patient's assessment (clear/nearly clear) at 4-6 weeks

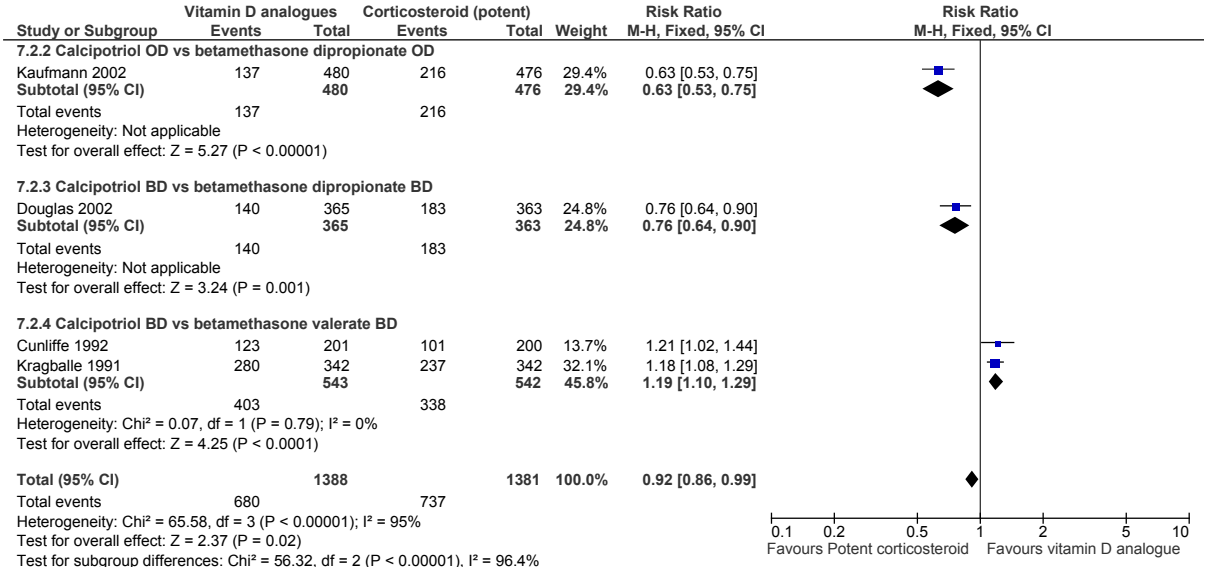


Figure 32: % change in PASI at 6-8 weeks

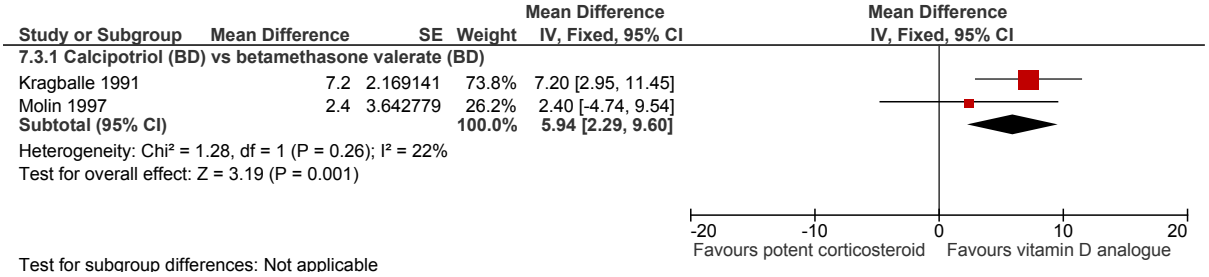


Figure 33: Relapse rate (8 weeks post-treatment)

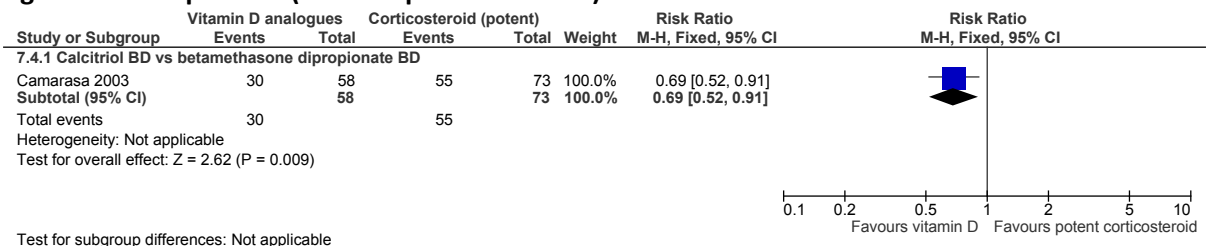


Figure 34: Withdrawals due to adverse events at 4-8 weeks

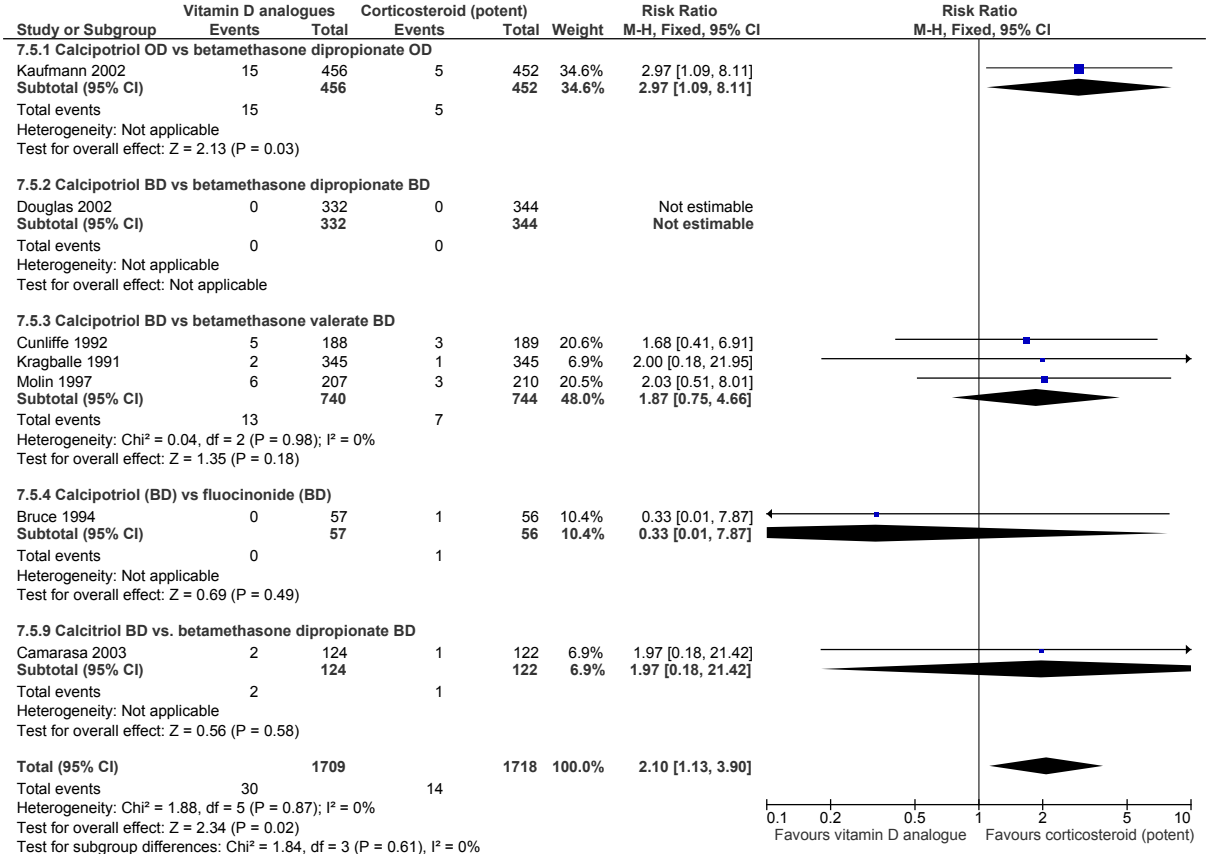


Figure 35: Withdrawal due to lack of efficacy at 6 weeks

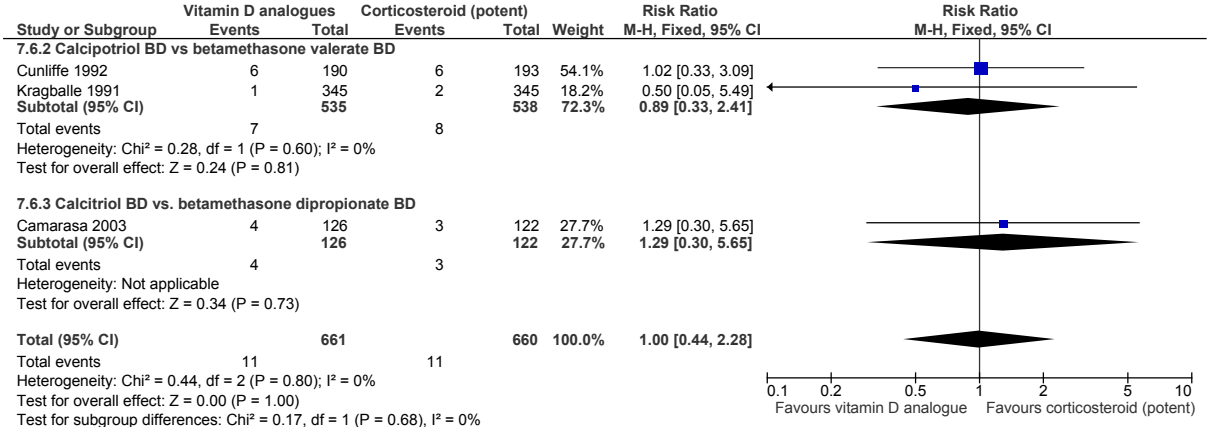
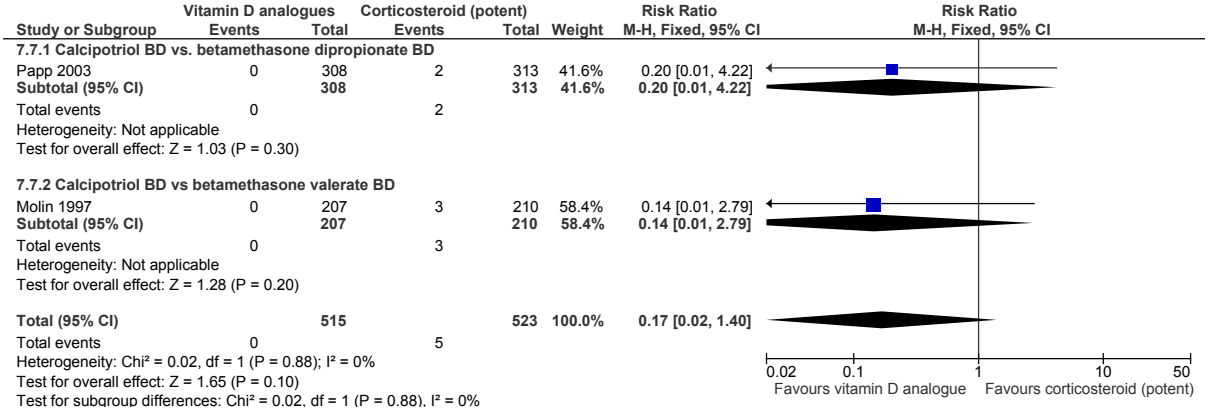
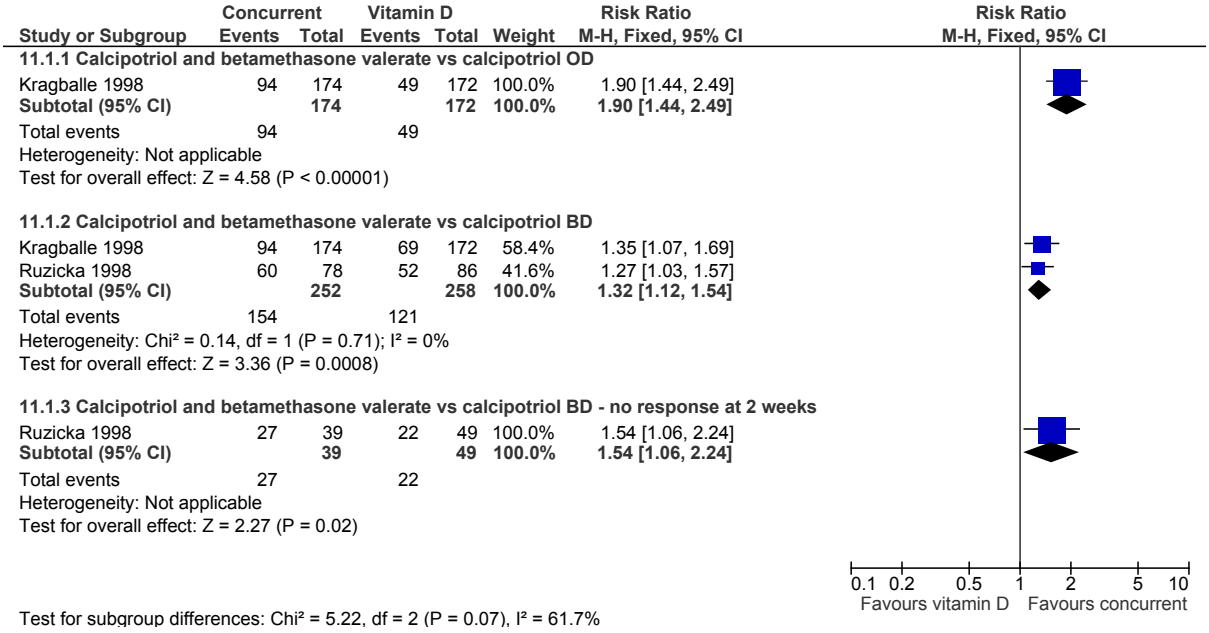


Figure 36: Skin atrophy at 4-8 weeks



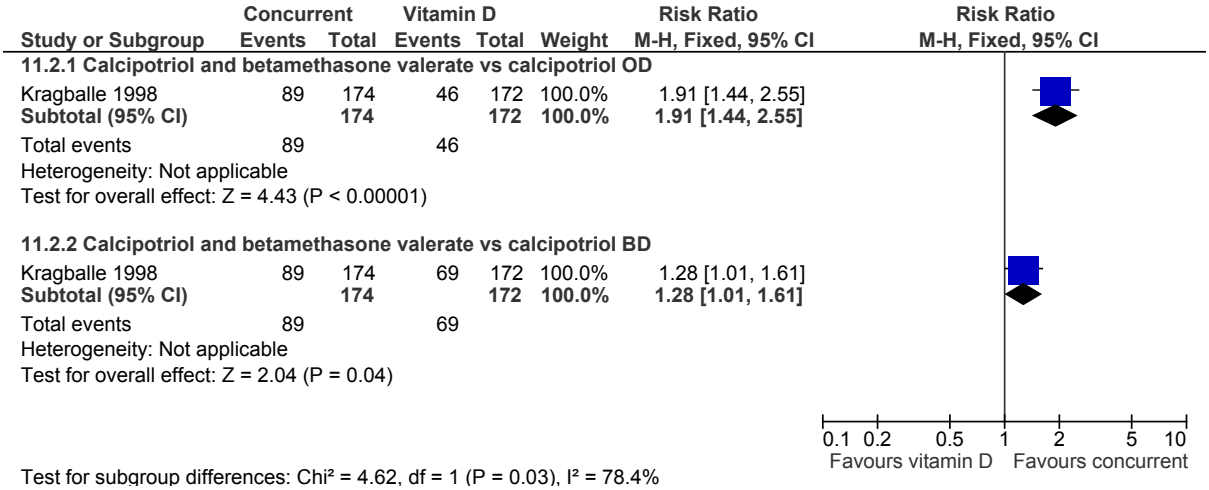
J.2.8 Concurrent vitamin D or vitamin D analogue and potent corticosteroid (one applied in the morning and one in the evening) vs vitamin D or vitamin D analogue alone

Figure 37: Investigator's assessment (clear/nearly clear) at 6-8 weeks



Test for subgroup differences: Chi² = 5.22, df = 2 (P = 0.07), I² = 61.7%

Figure 38: Patient's assessment (clear/nearly clear) at 8 weeks



Test for subgroup differences: Chi² = 4.62, df = 1 (P = 0.03), I² = 78.4%

Figure 39: Withdrawals due to adverse events at 4-8 weeks

Note: different scale

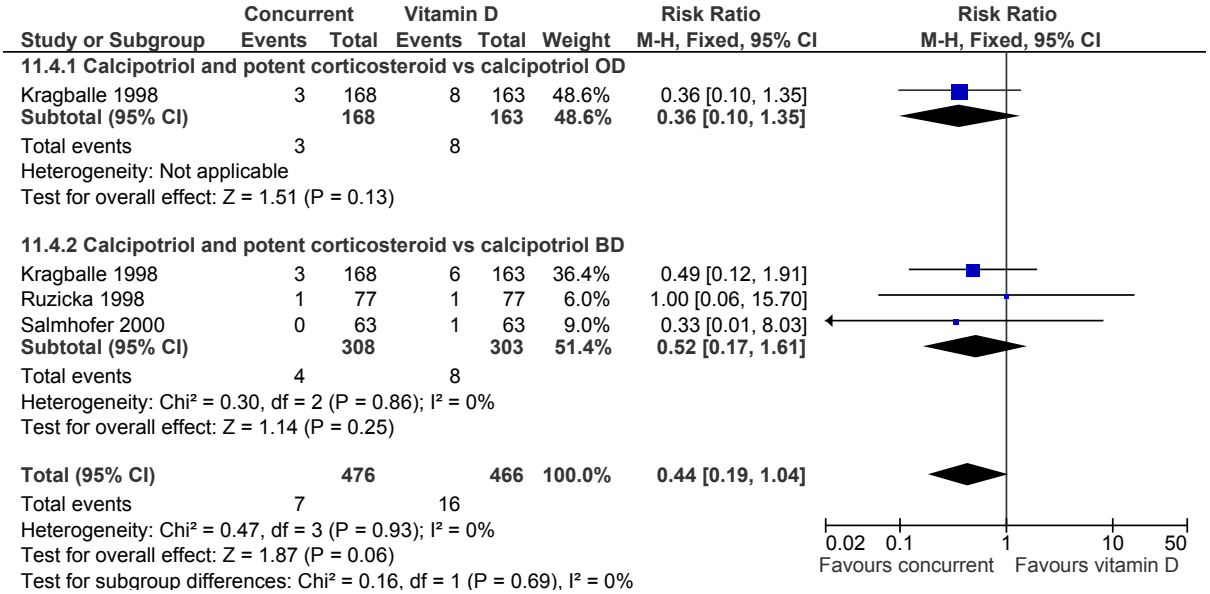
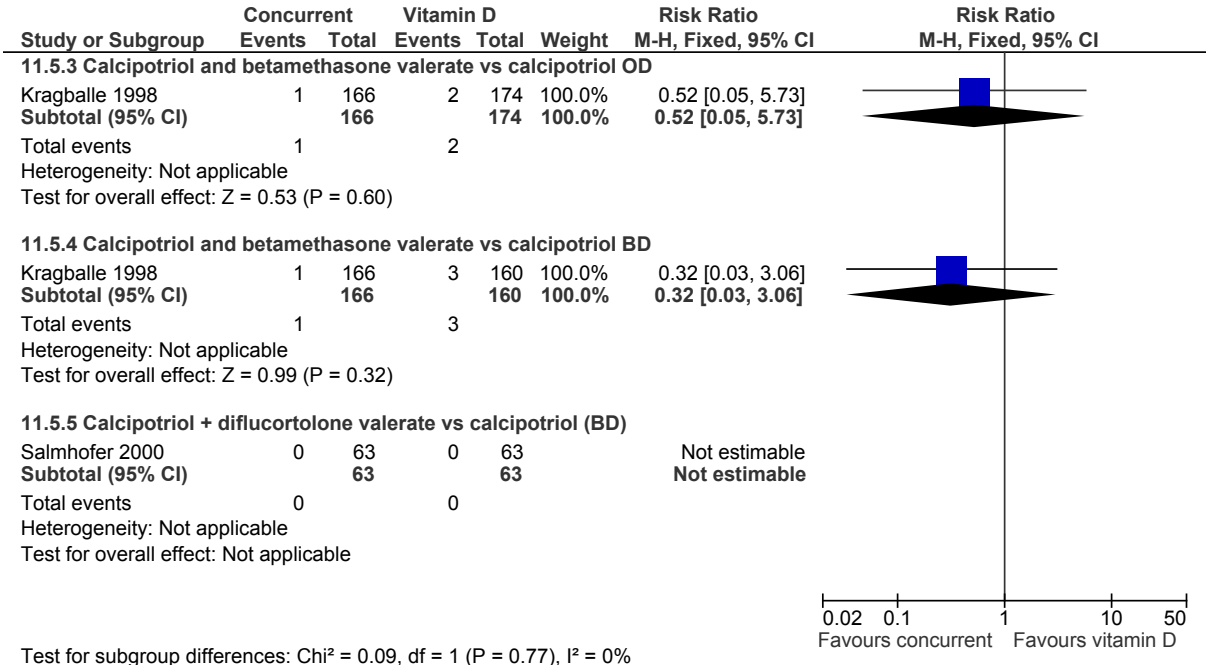


Figure 40: Withdrawal due to lack of efficacy at 4-8 weeks

Note: different scale



J.2.9 Combined product containing potent corticosteroid and vitamin D analogue vs vitamin D or vitamin D analogue

Figure 41: Investigator's assessment (clear/nearly clear) at 4-8 weeks

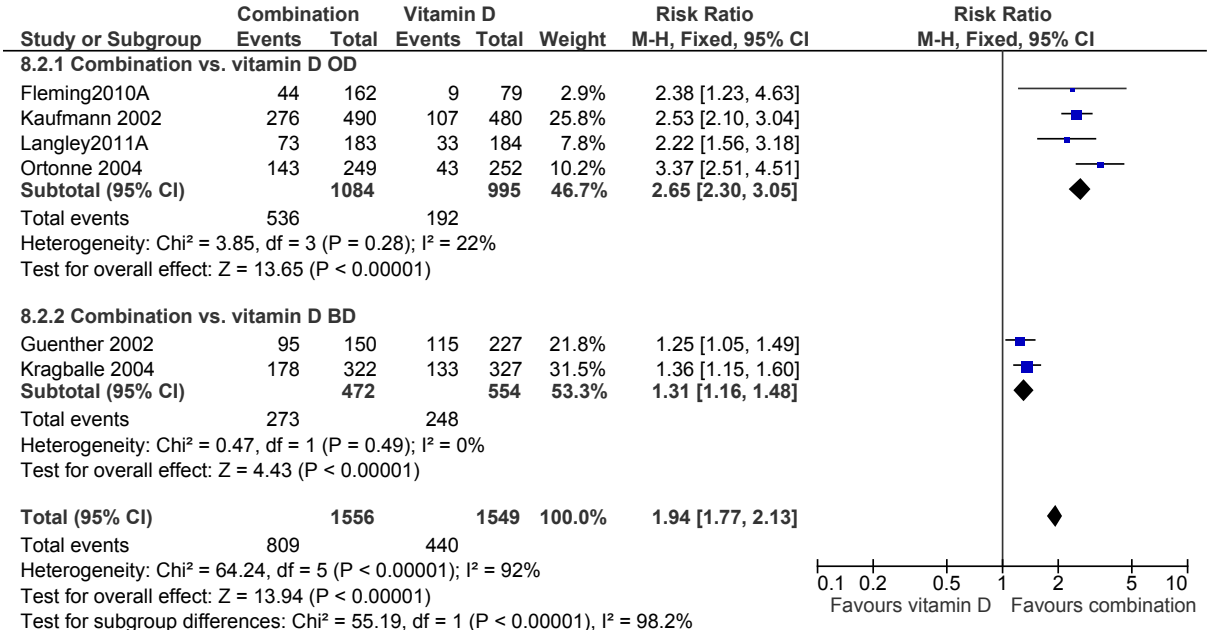


Figure 42: Patient's assessment (clear/nearly clear) at 4-8 weeks

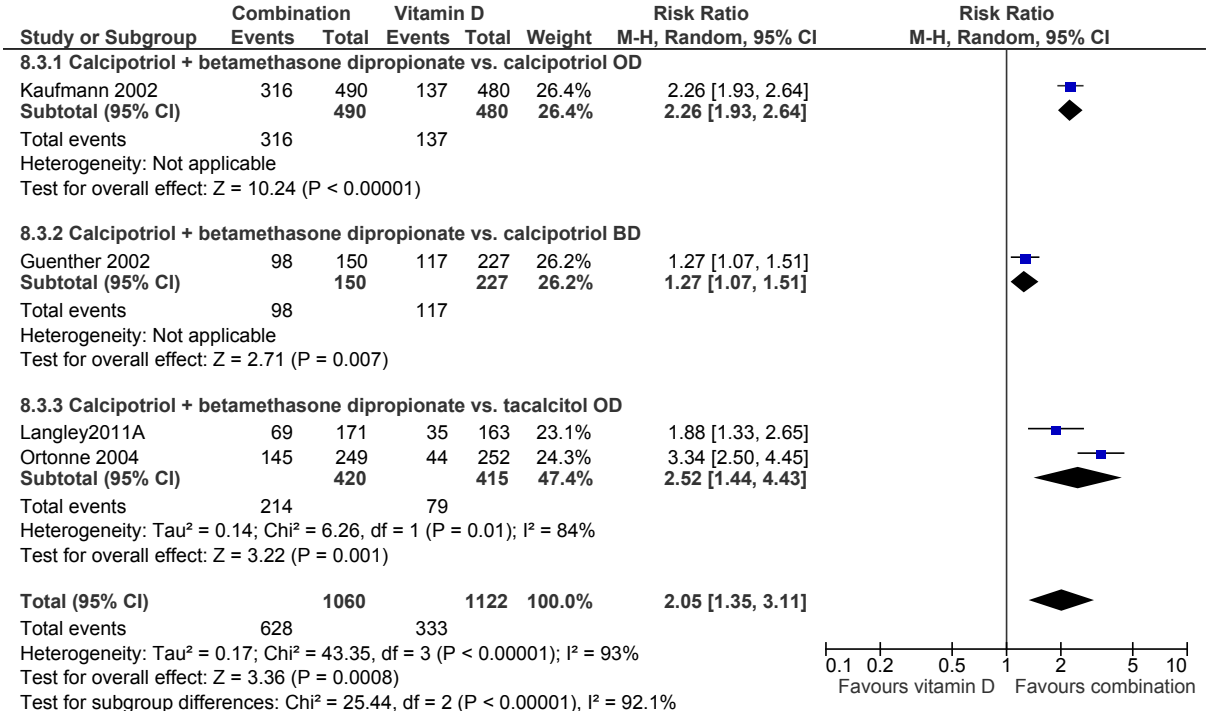


Figure 43: % change in PASI at 4-8 weeks

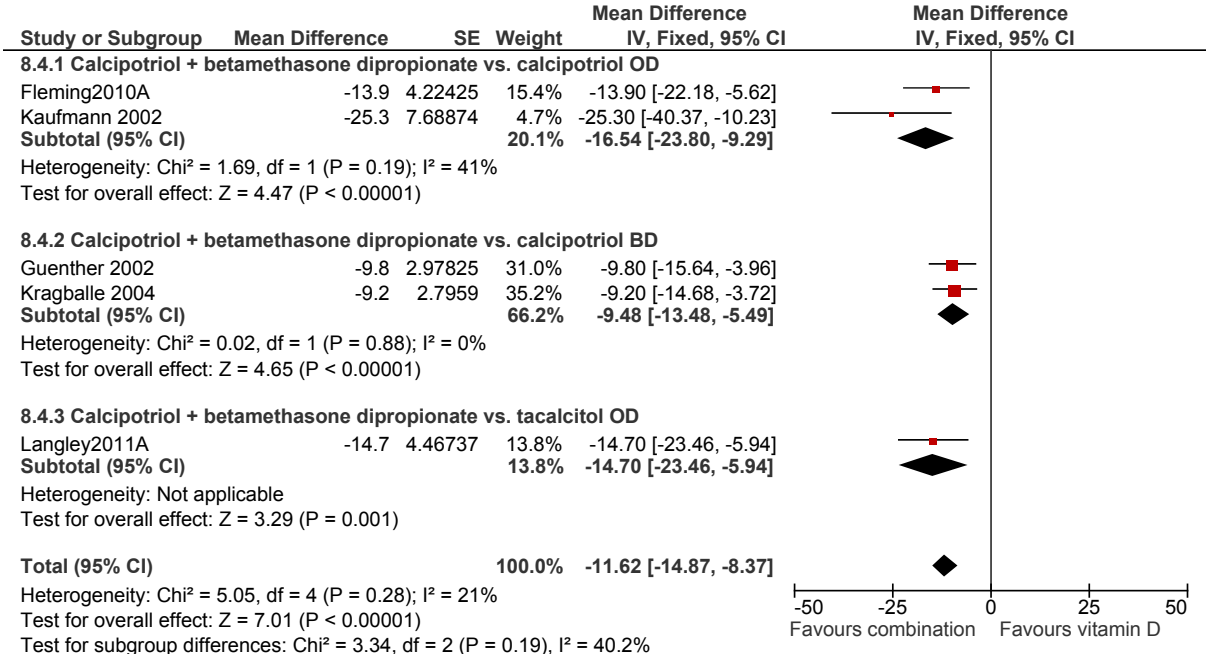


Figure 44: Relapse rate at 8 weeks post-treatment

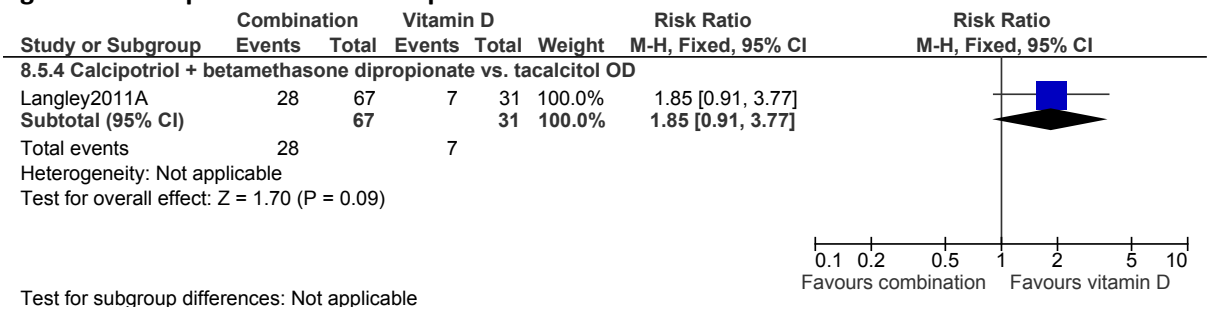


Figure 45: Withdrawal due to adverse events at 4-8 weeks

Note: different scale

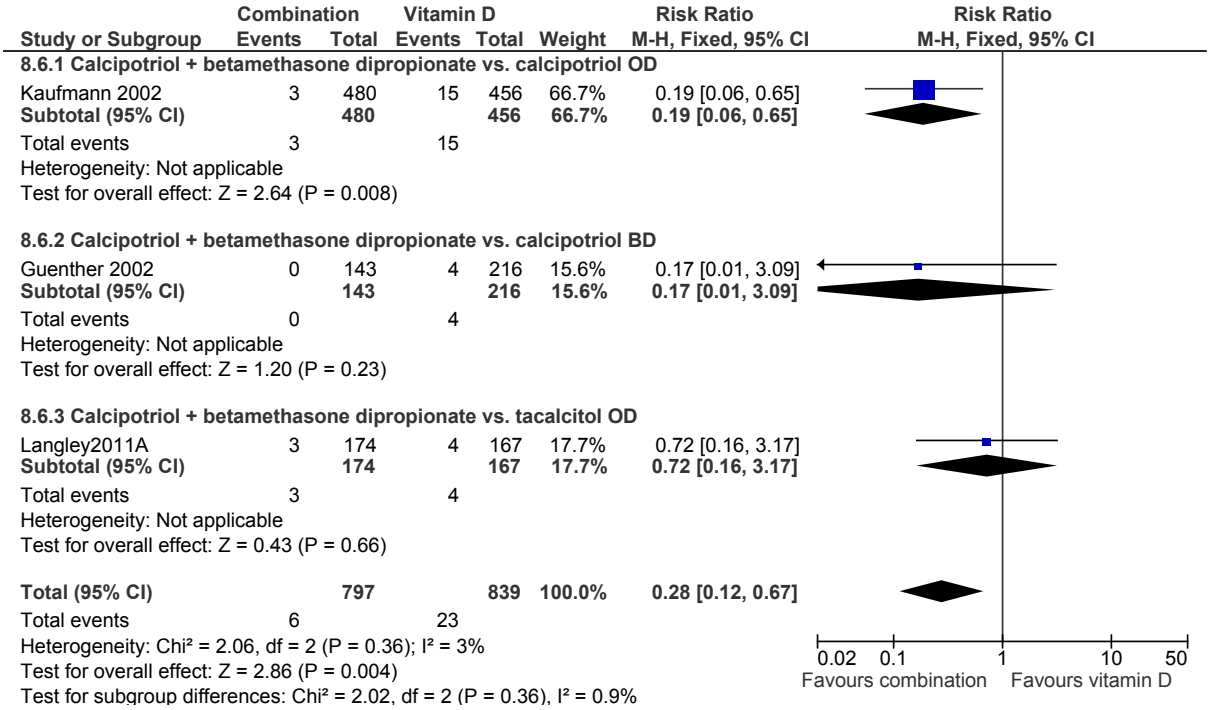


Figure 46: Withdrawal due to lack of efficacy at 4 weeks

Note: different scale

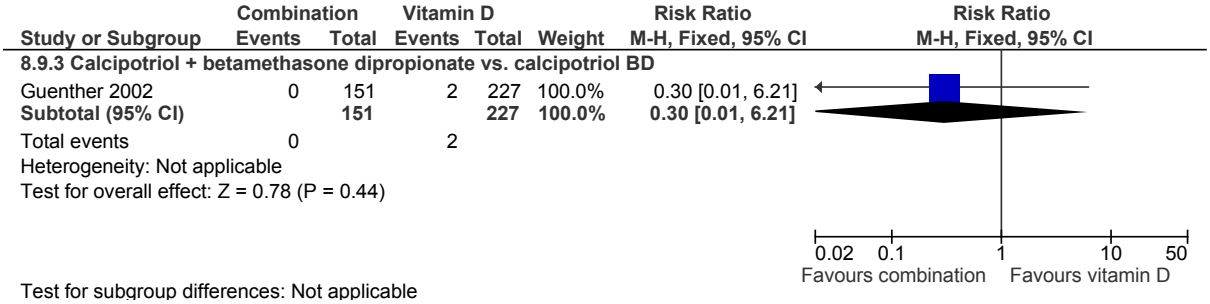
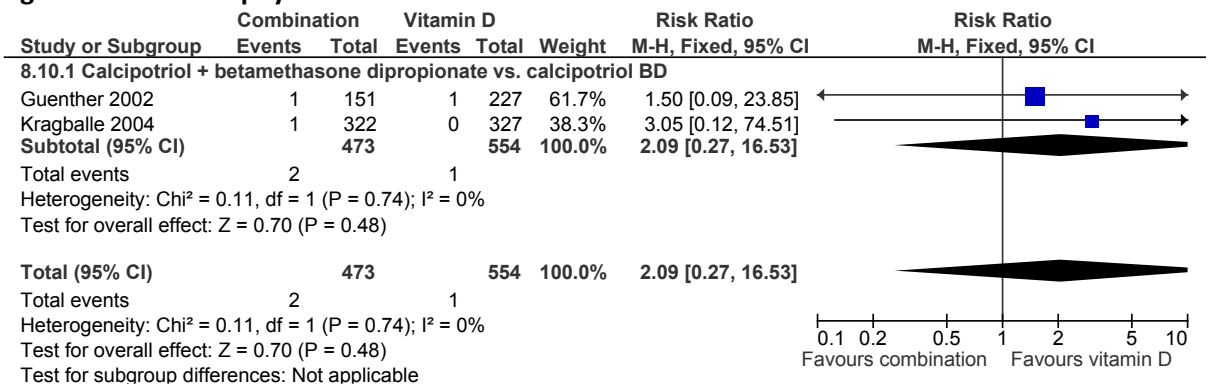


Figure 47: Skin atrophy at 4-12 weeks



J.2.10 Combined product containing vitamin D analogue and potent corticosteroid vs potent corticosteroid

Figure 48: Investigator's assessment (clear/nearly clear) at 4-8 weeks

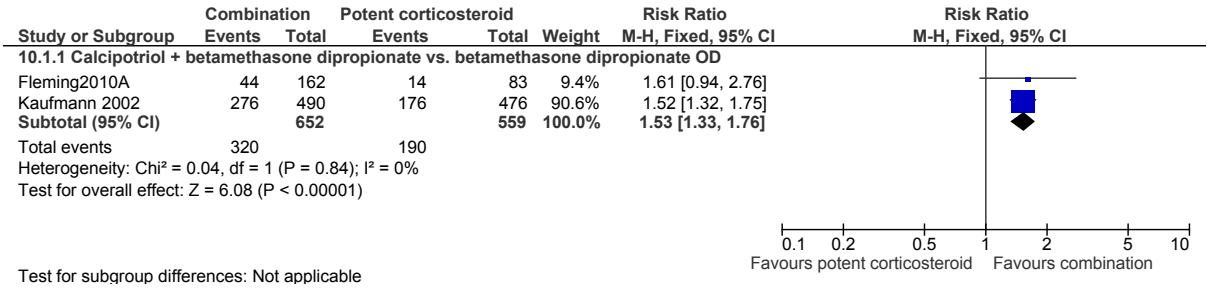


Figure 49: Patient's assessment (clear/nearly clear) at 4 weeks

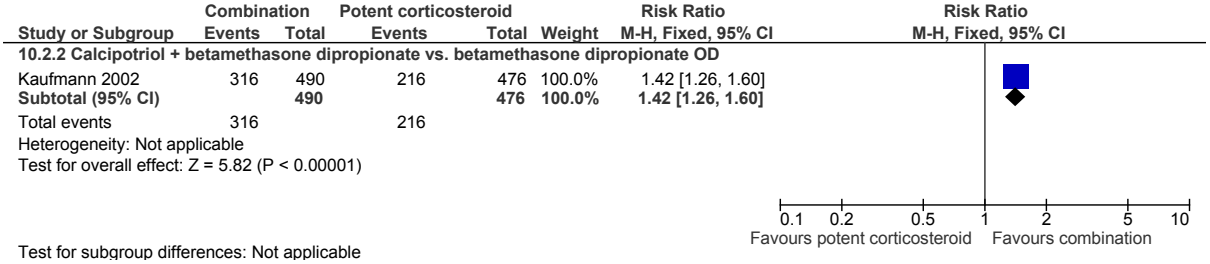


Figure 50: % change in PASI at 4-8 weeks

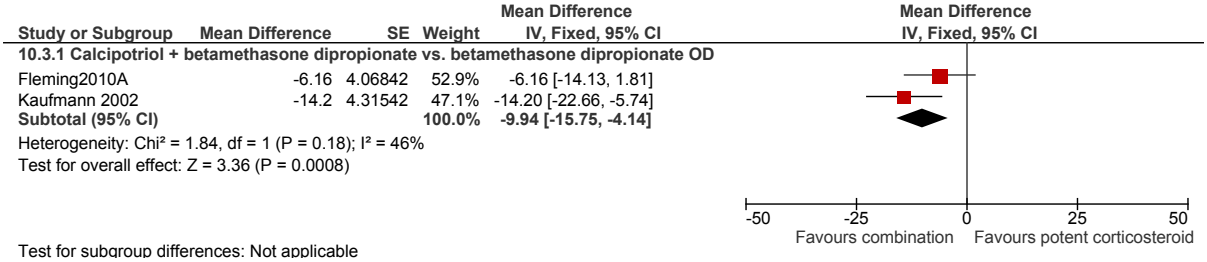
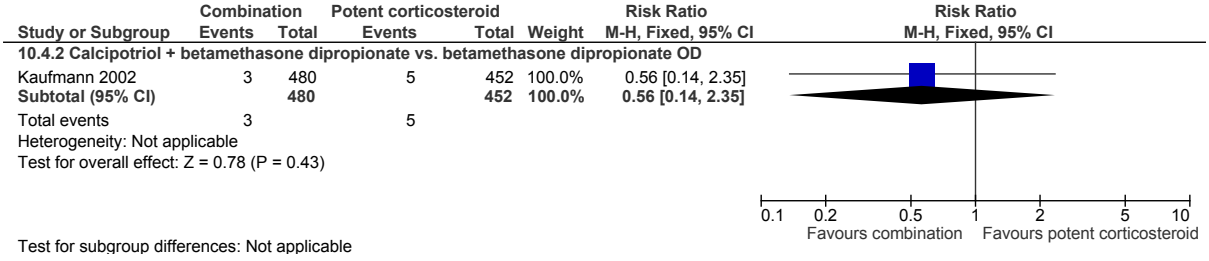


Figure 51: Withdrawals due to adverse events at 4 weeks



J.2.11 Combined product containing vitamin D analogue and potent corticosteroid *then* vitamin D or vitamin D analogue vs vitamin D or vitamin D analogue

Figure 52: Investigator's assessment (clear/nearly clear) at 8-12 weeks

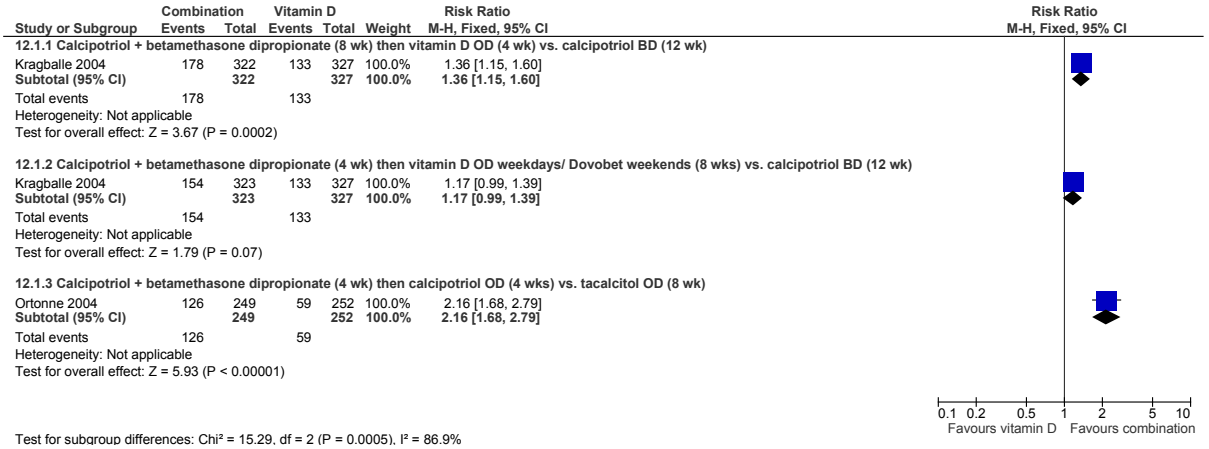


Figure 53: Patient's assessment (clear/nearly clear) at 8 weeks

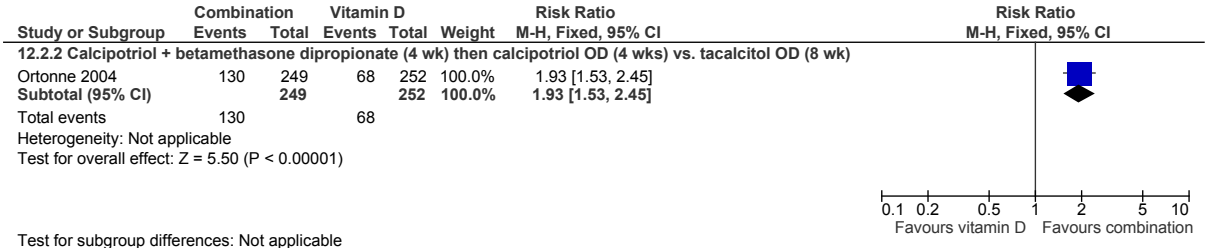


Figure 54: % change in PASI at 8-12 weeks

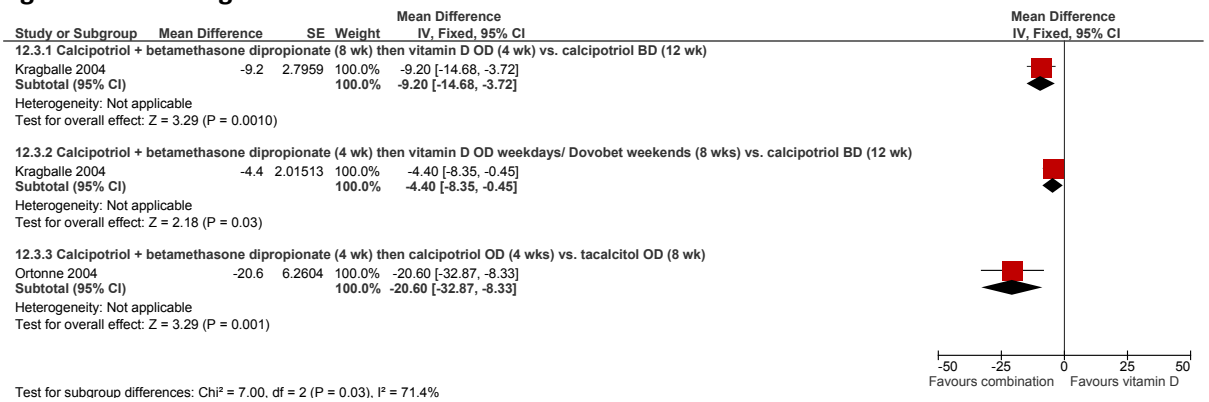


Figure 55: Withdrawal due to adverse events at 8-12 weeks

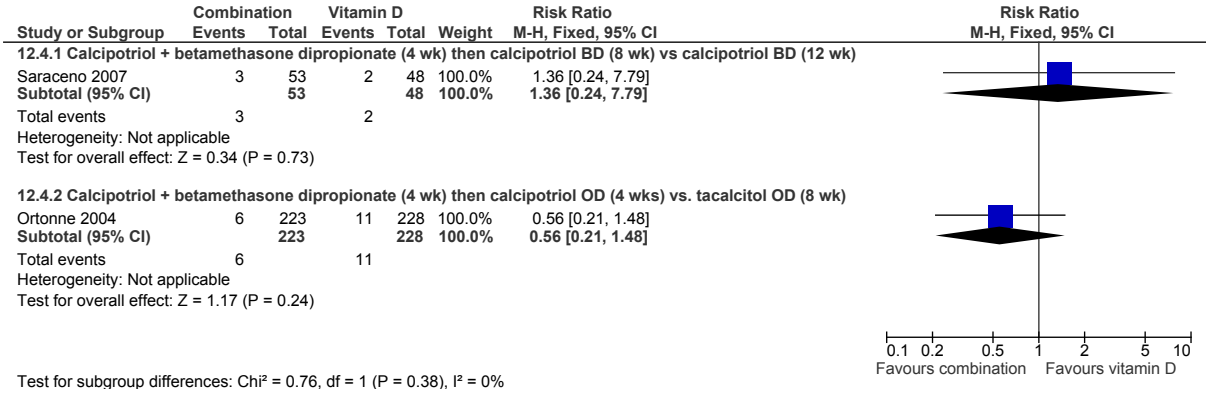


Figure 56: Withdrawal due to lack of efficacy at 8-12 weeks

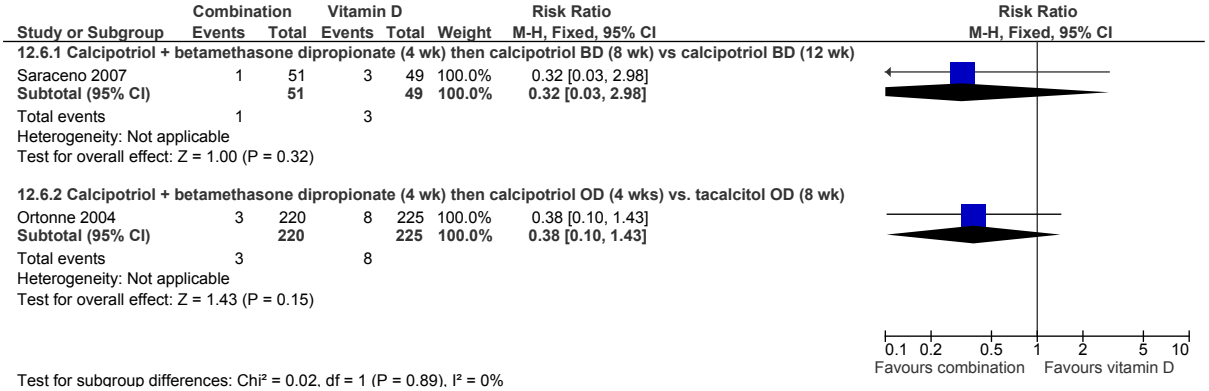
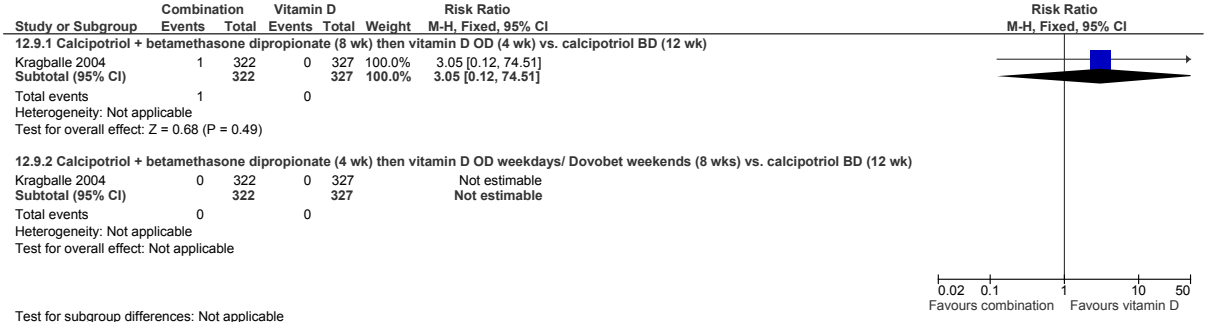


Figure 57: Skin atrophy at 12 weeks



J.2.12 Combined product containing potent corticosteroid and vitamin D analogue vs vitamin D or vitamin D analogue (for maintenance of remission)

Figure 58: Investigator's assessment (clear/nearly clear) at 52 weeks

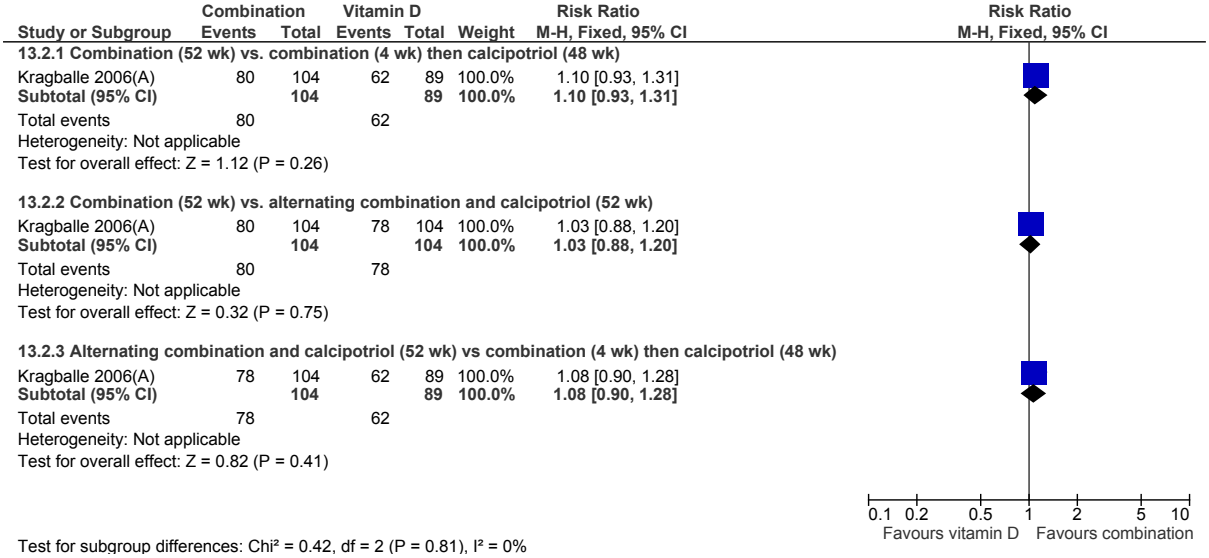


Figure 59: Skin atrophy at 52 weeks

Note: different scale

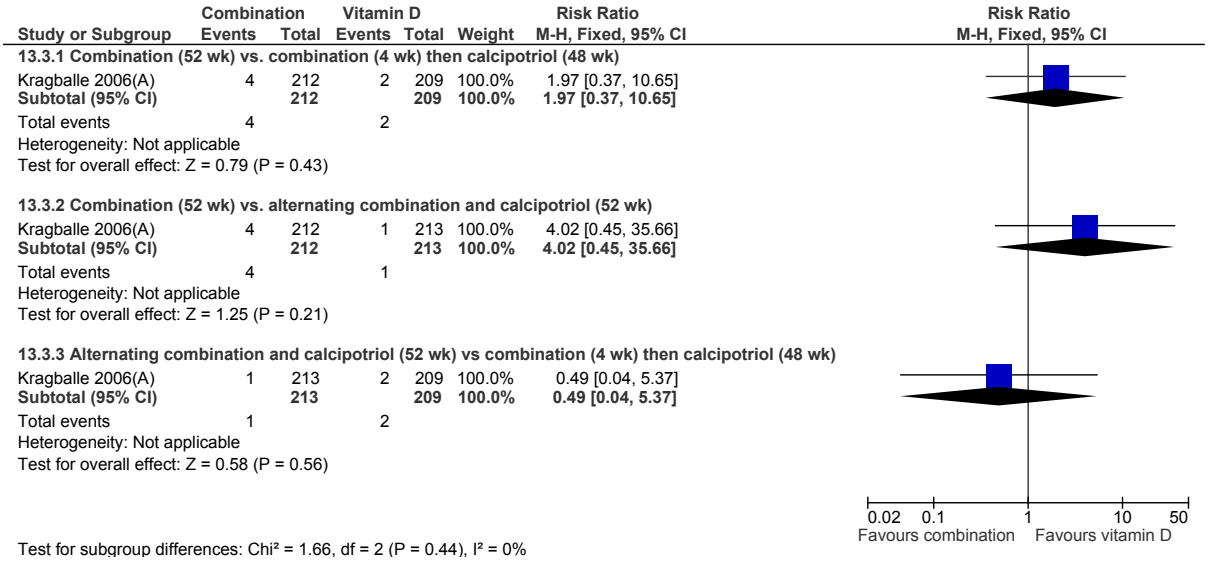


Figure 60: Withdrawal due to adverse events at 52 weeks

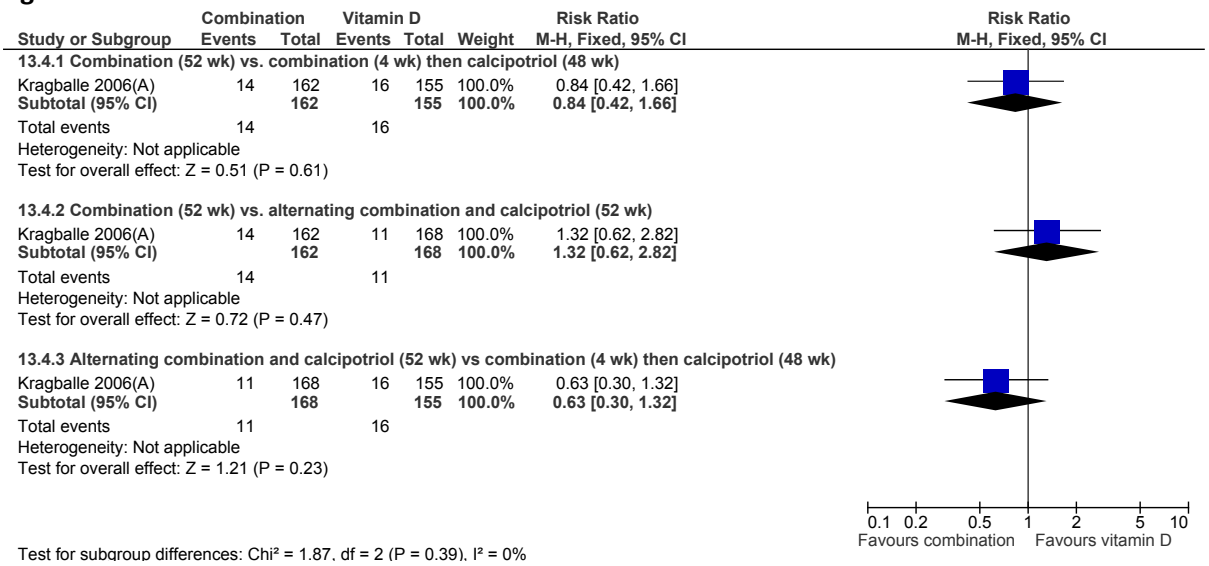
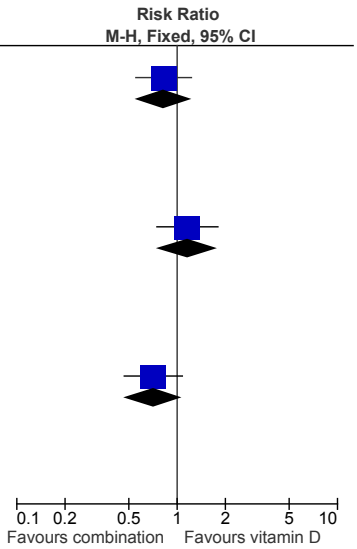


Figure 61: Withdrawal due to lack of efficacy at 52 weeks

Study or Subgroup	Combination Events	Total	Vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.6.1 Combination (52 wk) vs. combination (4 wk) then calcipotriol (48 wk)						
Kragballe 2006(A)	35	183	42	181	100.0%	0.82 [0.55, 1.23]
Subtotal (95% CI)		**183**		**181**	**100.0%**	**0.82 [0.55, 1.23]**
Total events	35		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
13.6.2 Combination (52 wk) vs. alternating combination and calcipotriol (52 wk)						
Kragballe 2006(A)	35	183	31	188	100.0%	1.16 [0.75, 1.80]
Subtotal (95% CI)		**183**		**188**	**100.0%**	**1.16 [0.75, 1.80]**
Total events	35		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
13.6.3 Alternating combination and calcipotriol (52 wk) vs combination (4 wk) then calcipotriol (48 wk)						
Kragballe 2006(A)	31	188	42	181	100.0%	0.71 [0.47, 1.08]
Subtotal (95% CI)		**188**		**181**	**100.0%**	**0.71 [0.47, 1.08]**
Total events	31		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						

Test for subgroup differences: Chi² = 2.63, df = 2 (P = 0.27), I² = 23.9%



J.2.13 Vitamin D or vitamin D analogue vs dithranol

Figure 62: Investigator's assessment (clear/nearly clear) at 8-12 weeks - calcipotriol

Study or Subgroup	Vitamin D analogue Events	Total	Dithranol Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.1.1 Calcipotriol BD vs. dithranol OD						
Berth Jones 1992	180	231	116	227	54.5%	1.52 [1.32, 1.76]
Christensen 1999	6	89	4	77	2.9%	1.30 [0.38, 4.43]
Wall 1998	92	153	67	131	42.5%	1.18 [0.95, 1.45]
Subtotal (95% CI)		**473**		**435**	**100.0%**	**1.36 [1.10, 1.68]**
Total events	278		187			
Heterogeneity: Tau² = 0.02; Chi² = 4.00, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Total (95% CI)		**473**		**435**	**100.0%**	**1.36 [1.10, 1.68]**
Total events	278		187			
Heterogeneity: Tau² = 0.02; Chi² = 4.00, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Test for subgroup differences: Not applicable						

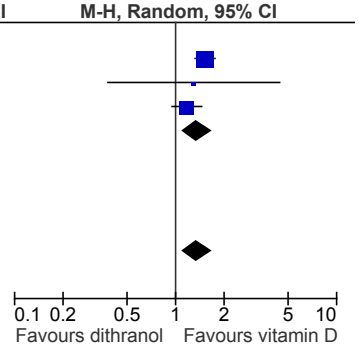


Figure 63: Investigator's assessment (clear/nearly clear) at 8 weeks - calcitriol

Study or Subgroup	Vitamin D analogue Events	Total	Dithranol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.2.3 Calcitriol BD vs. dithranol OD						
Hutchinson 2000	4	60	9	54	100.0%	0.40 [0.13, 1.22]
Subtotal (95% CI)		**60**		**54**	**100.0%**	**0.40 [0.13, 1.22]**
Total events	4		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						

Test for subgroup differences: Not applicable

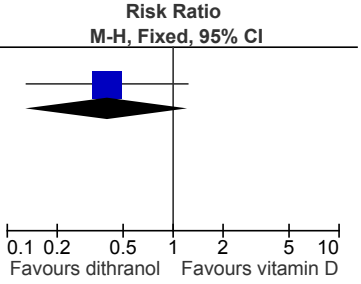


Figure 64: Patient's assessment (clear/nearly clear) at 8-12 weeks

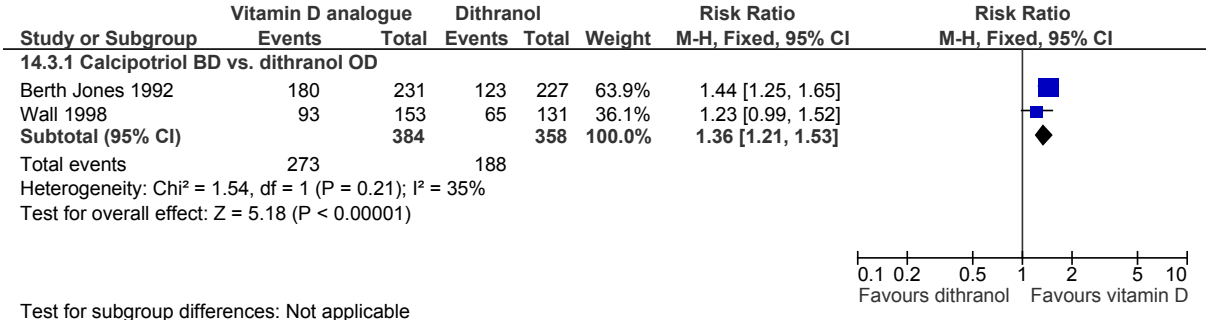


Figure 65: % change in PASI at 8 weeks

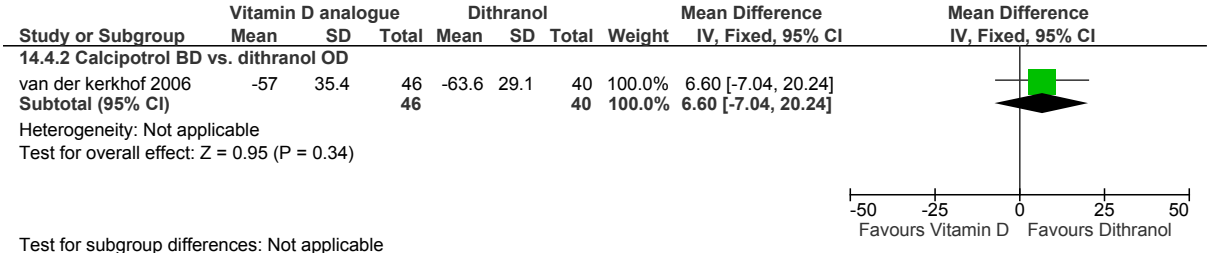


Figure 66: Withdrawal due to adverse events at 8-12 weeks

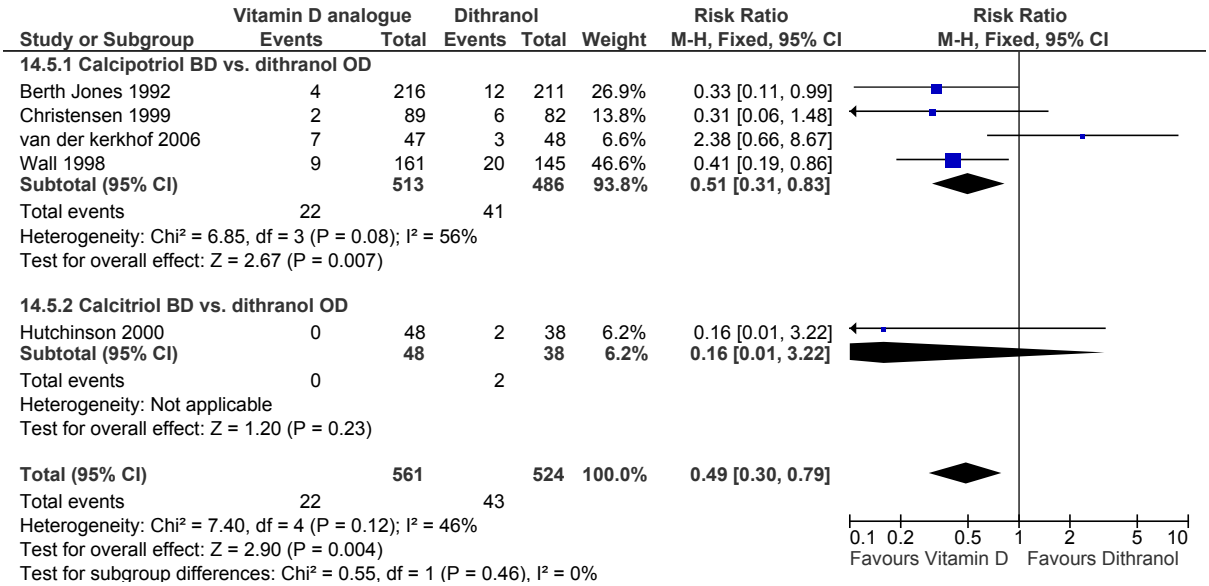


Figure 67: Withdrawal due to lack of efficacy at 8 weeks

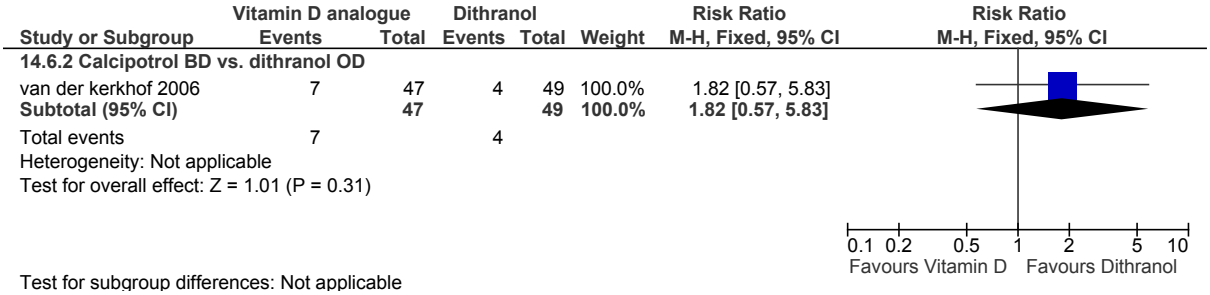
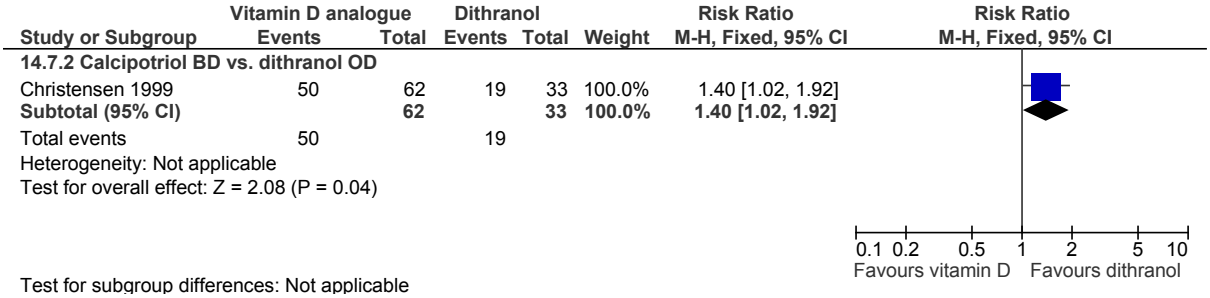


Figure 68: Relapse rate (8 weeks post-treatment)



J.2.14 Vitamin D or vitamin D analogue vs coal tar

Figure 69: Investigator's assessment (clear/nearly clear) at 6-12 weeks

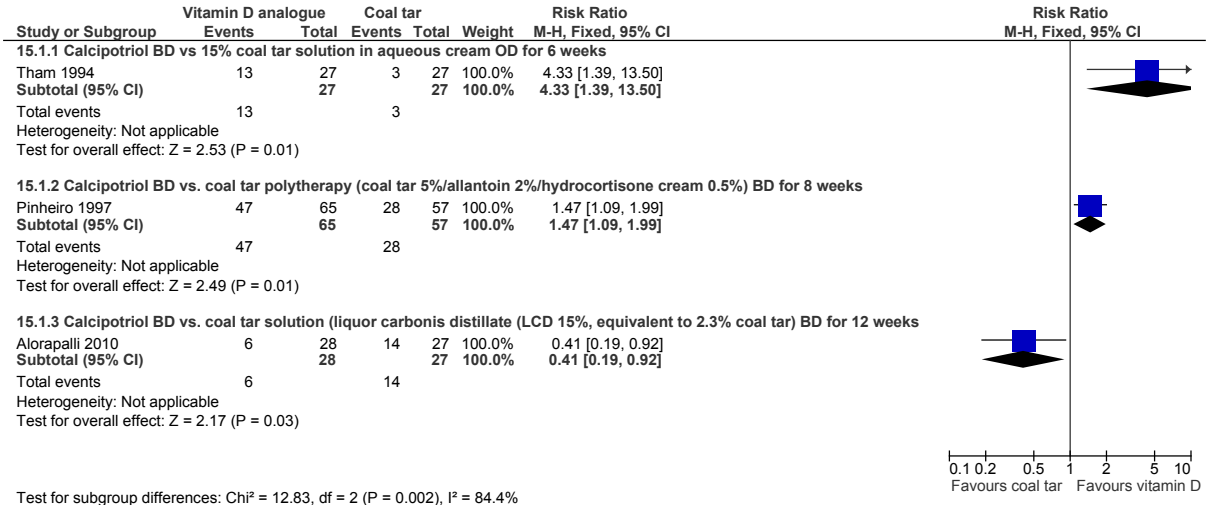


Figure 70: % change in PASI at 6-12 weeks

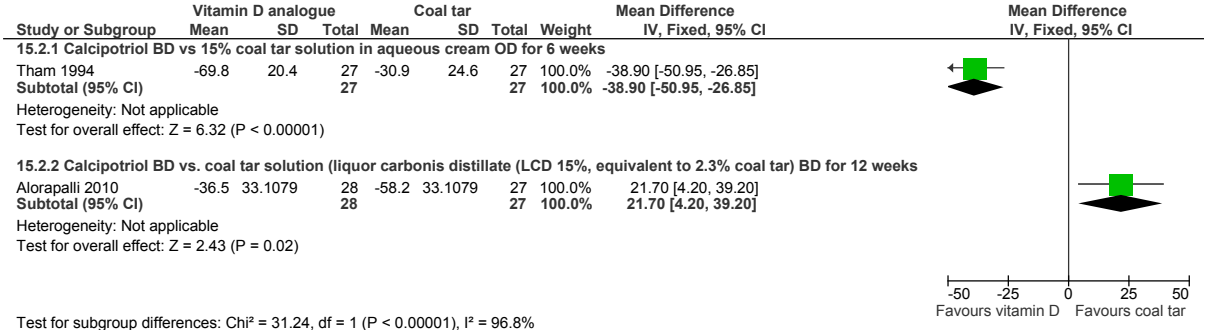


Figure 71: Relapse rate (6 weeks post treatment)

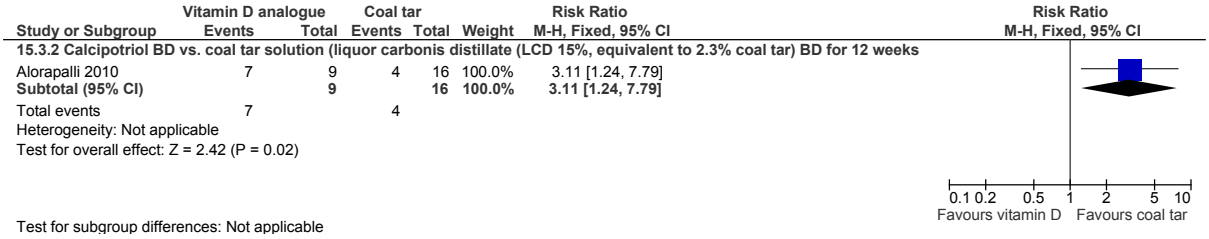
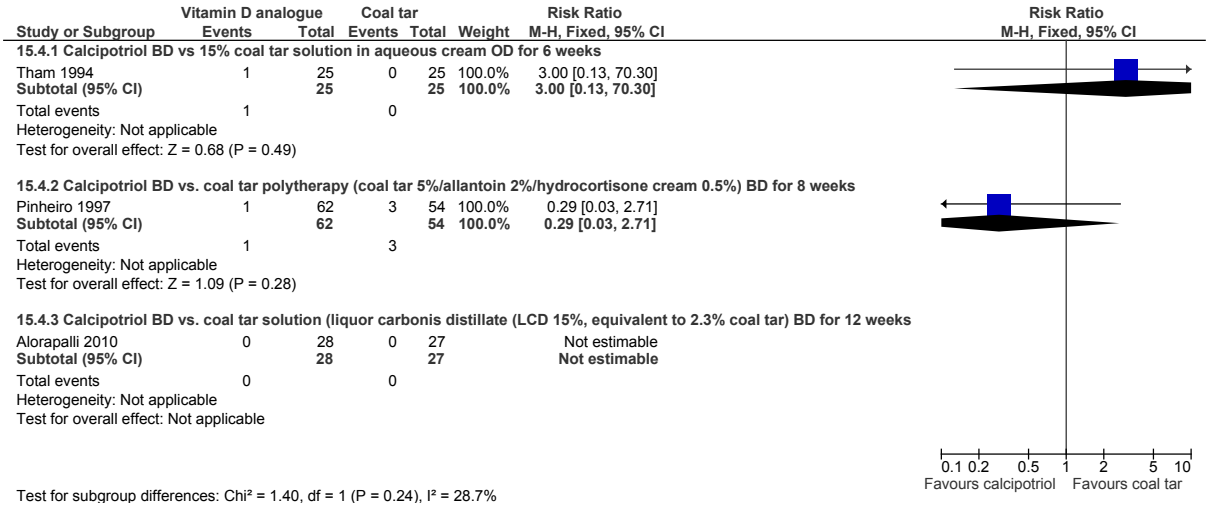


Figure 72: Withdrawal due to adverse events at 6-12 weeks



J.2.15 Vitamin D or vitamin D analogue once daily vs vitamin D or vitamin D analogue twice daily

Figure 73: Investigator's assessment (clear/nearly clear) at 8 weeks

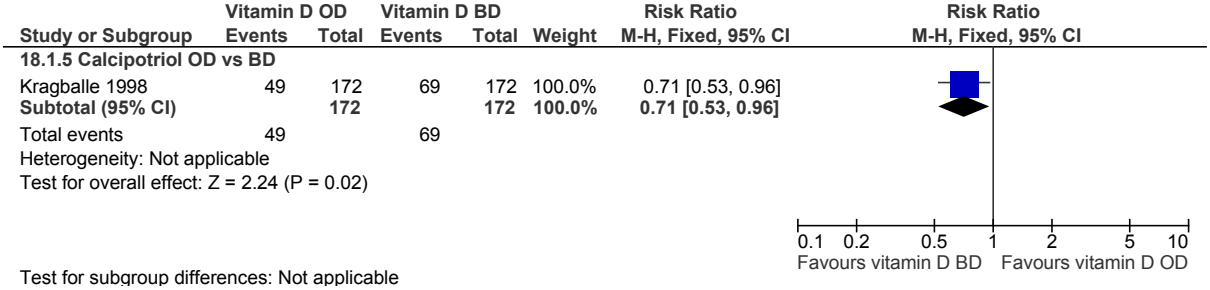
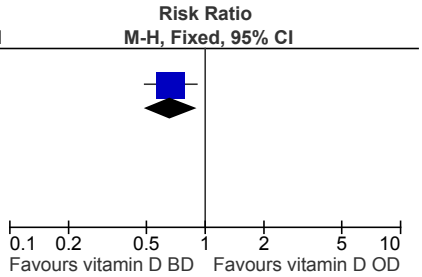


Figure 74: Patient's assessment (clear/nearly clear) at 8 weeks

Study or Subgroup	Vitamin D OD Events	Total	Vitamin D BD Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
18.2.5 Calcipotriol OD vs BD						
Kragballe 1998	46	172	69	172	100.0%	0.67 [0.49, 0.91]
Subtotal (95% CI)		**172**		**172**	**100.0%**	**0.67 [0.49, 0.91]**
Total events	46		69			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.58 (P = 0.010)

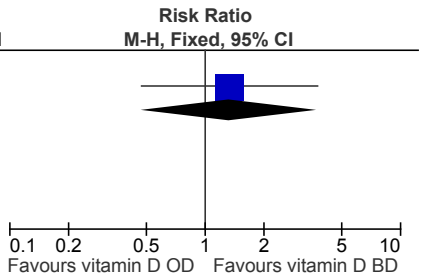


Test for subgroup differences: Not applicable

Figure 75: Withdrawal due to adverse events at 8 weeks

Study or Subgroup	Vitamin D OD Events	Total	Vitamin D BD Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
18.5.5 Calcipotriol OD vs BD						
Kragballe 1998	8	174	6	174	100.0%	1.33 [0.47, 3.76]
Subtotal (95% CI)		**174**		**174**	**100.0%**	**1.33 [0.47, 3.76]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

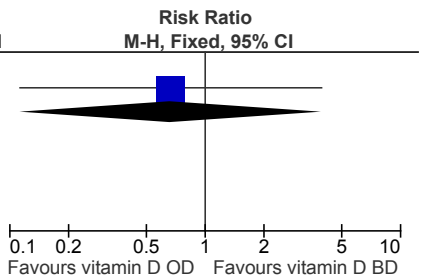


Test for subgroup differences: Not applicable

Figure 76: Withdrawal due to lack of efficacy at 8 weeks

Study or Subgroup	Vitamin D OD Events	Total	Vitamin D BD Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
18.8.5 Calcipotriol OD vs BD						
Kragballe 1998	2	174	3	174	100.0%	0.67 [0.11, 3.94]
Subtotal (95% CI)		**174**		**174**	**100.0%**	**0.67 [0.11, 3.94]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



Test for subgroup differences: Not applicable

J.3 Topicals – difficult to treat sites (face, flexures and scalp)

J.3.1 Scalp: Vitamin D or vitamin D analogue vs placebo

Figure 77: Investigator's assessment (clear/nearly clear) at 4-8 weeks

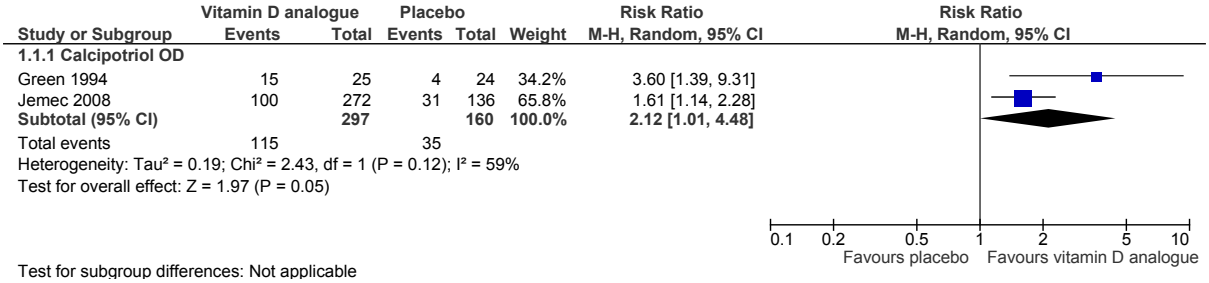


Figure 78: Patient's assessment (clear/nearly clear) at 8 weeks

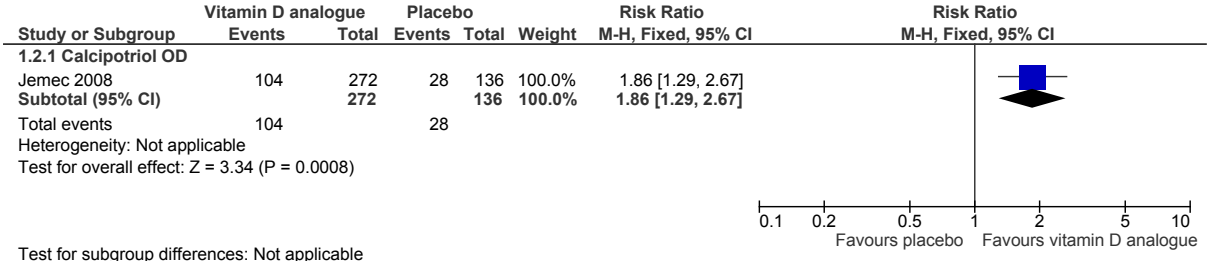


Figure 79: Withdrawals due to adverse events at 4-8 weeks

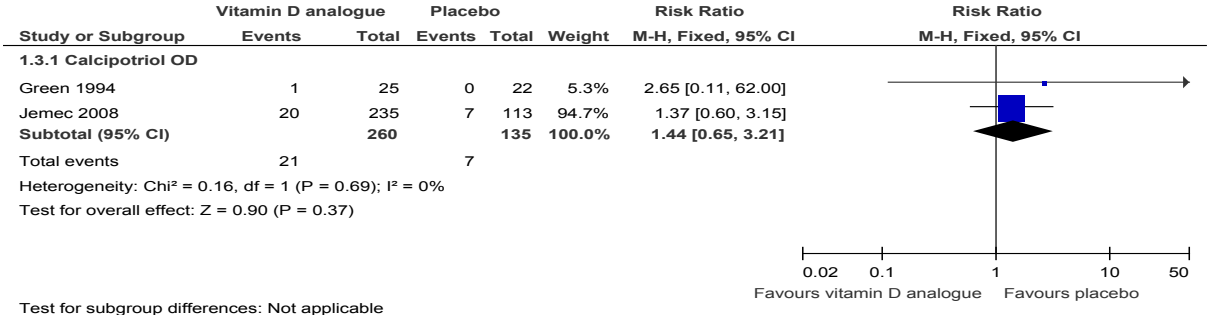
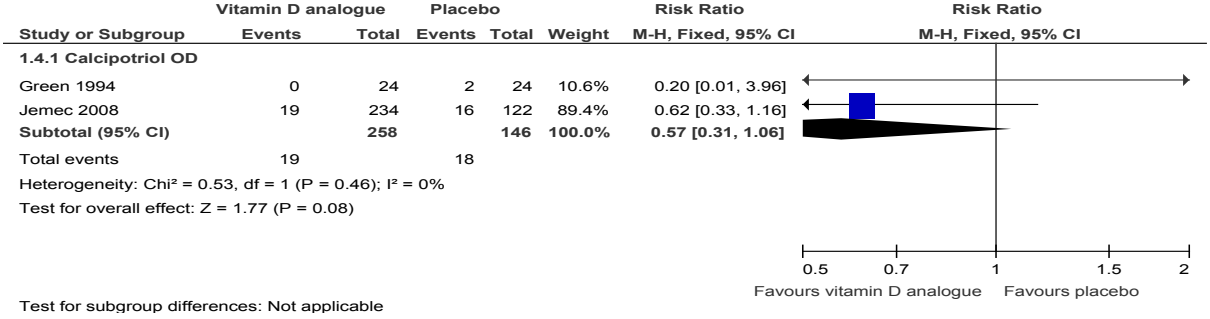


Figure 80: Withdrawals due to lack of efficacy at 4-8 weeks



J.3.2 Scalp: Potent corticosteroid vs placebo

Figure 81: Investigator's assessment (clear/nearly clear) at 4-8 weeks

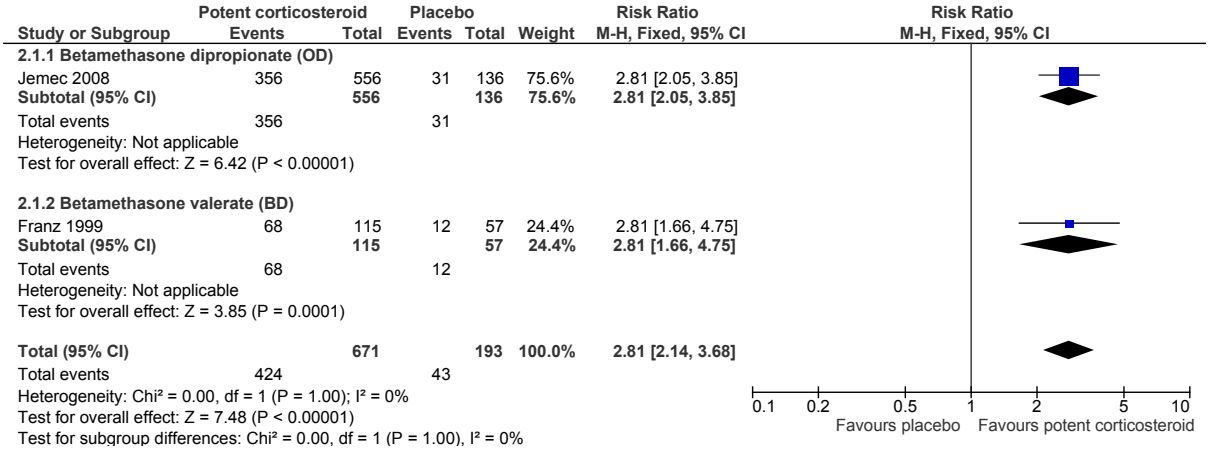


Figure 82: Patient's assessment (clear/nearly clear) at 4-8 weeks

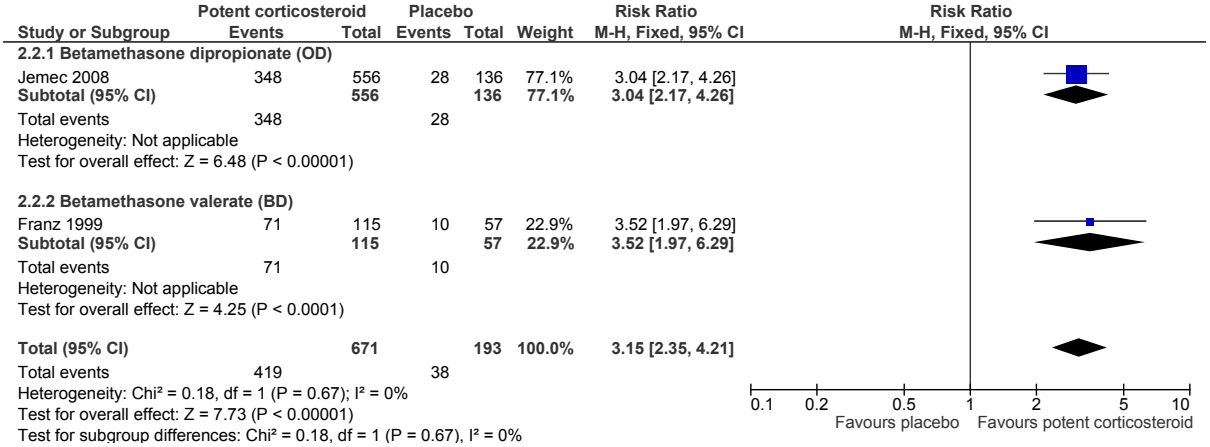


Figure 83: Withdrawals due to adverse events at 4-8 weeks

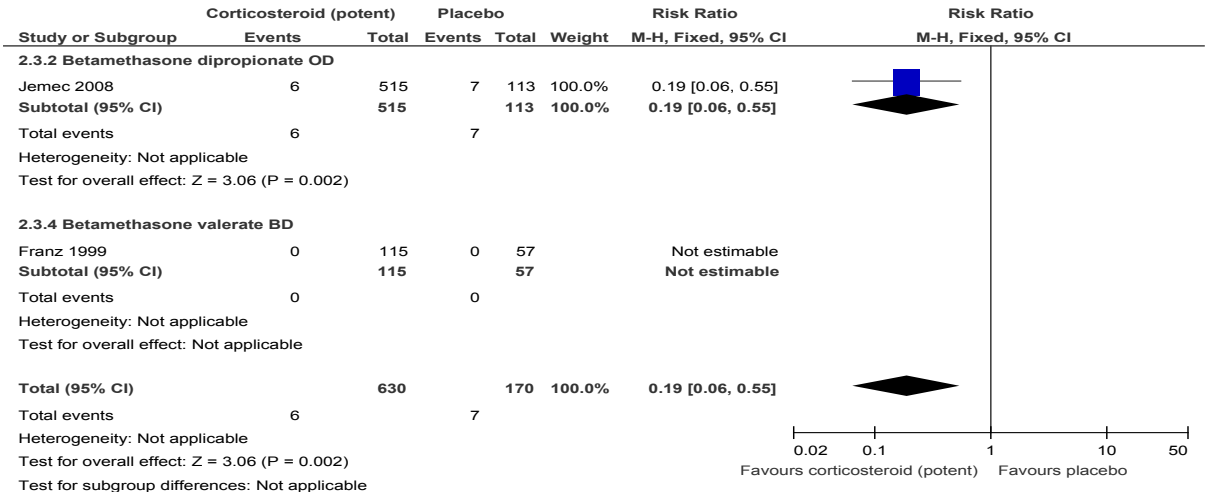
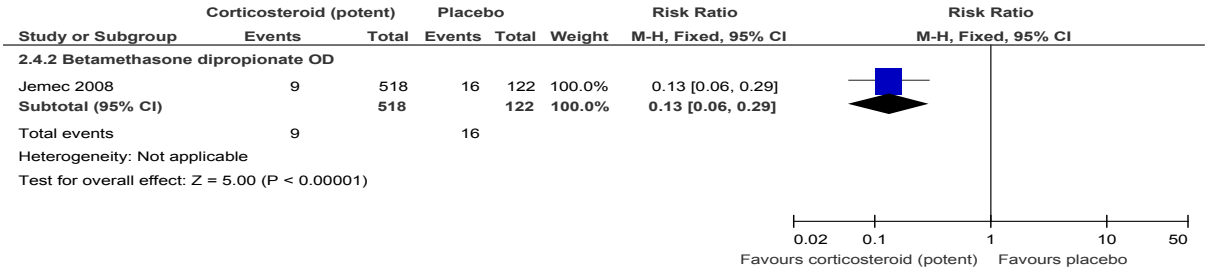


Figure 84: Withdrawals due to treatment failure at 8 weeks



J.3.3 Scalp: Very potent corticosteroid vs placebo

Figure 85: Investigator's assessment (clear/nearly clear) at 2-4 weeks

Note: different scale

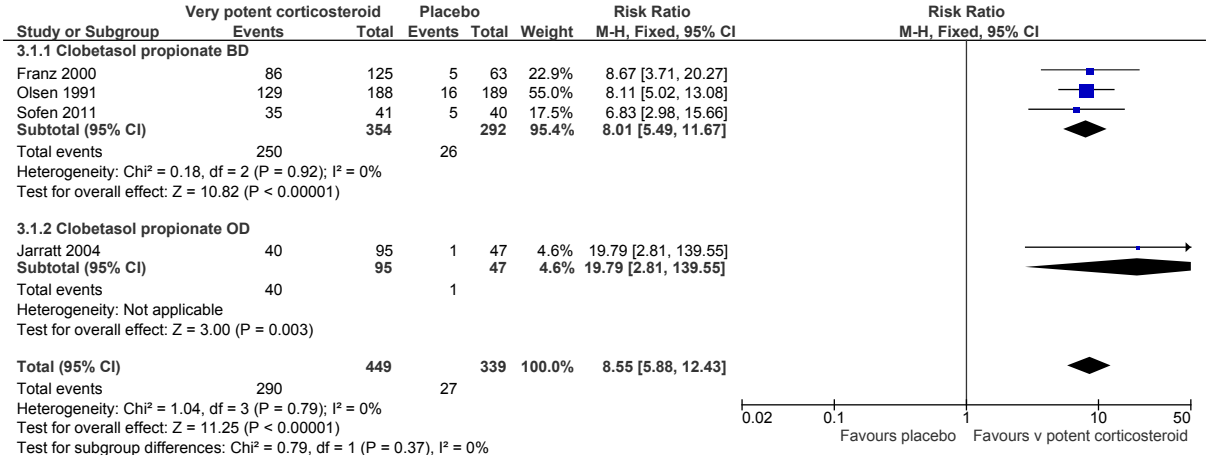


Figure 86: Patient's assessment (clear/nearly clear) at 2 weeks

Note: different scale

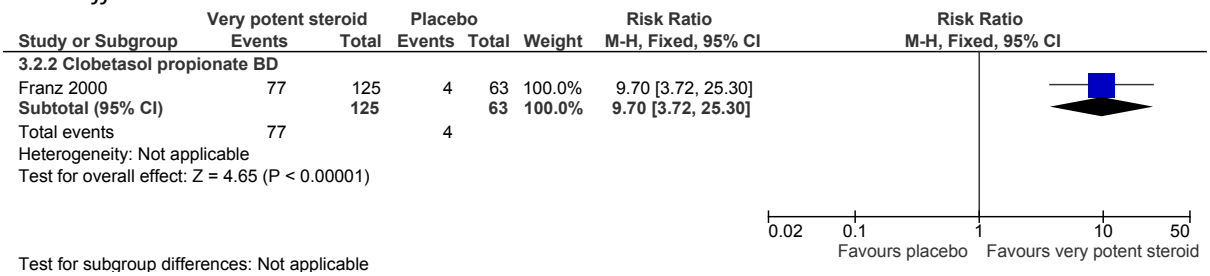


Figure 87: Skin atrophy at 4 weeks

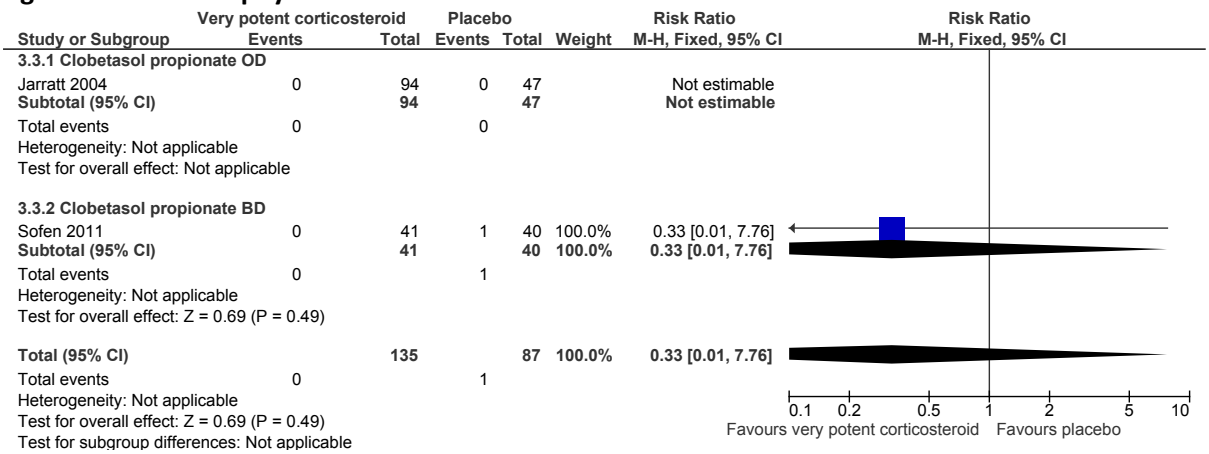


Figure 88: Withdrawals due to adverse events at 2-4 weeks

Note: different scale

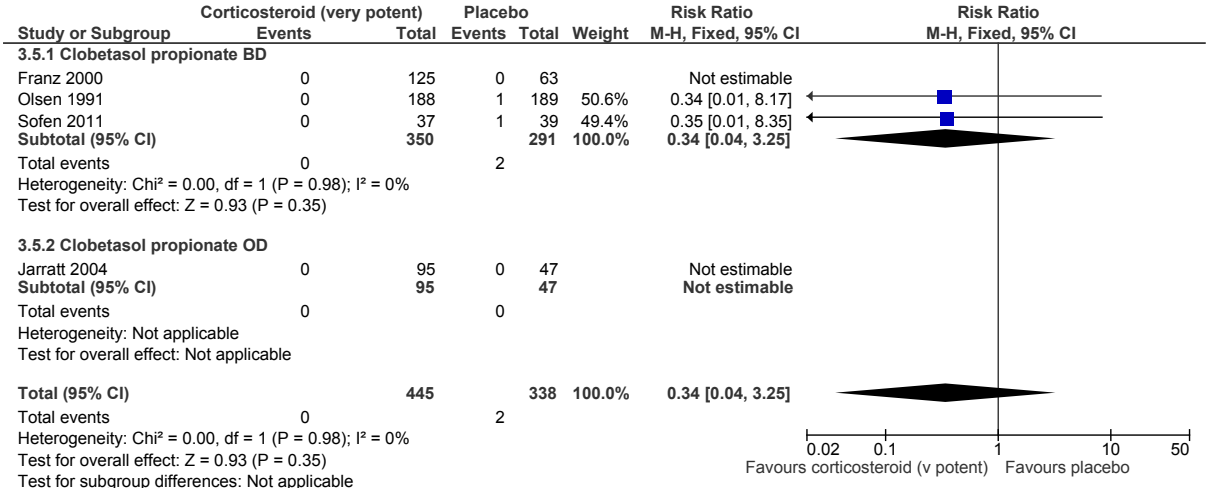
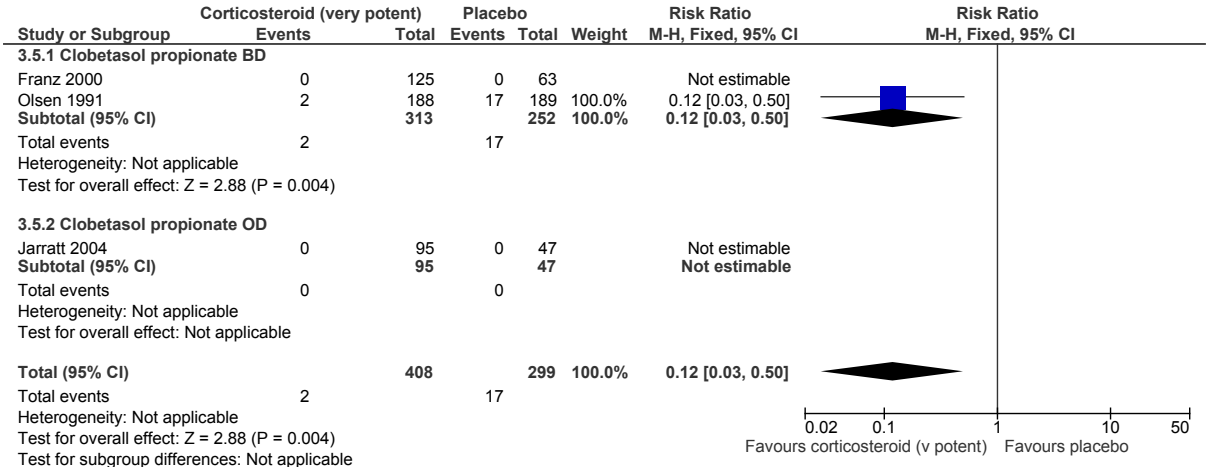


Figure 89: Withdrawals due to lack of efficacy at 2-4 weeks

Note: different scale



J.3.4 Scalp: Combined product containing potent corticosteroid and vitamin D analogue vs placebo

Figure 90: Investigator's assessment (clear/nearly clear) at 8 weeks

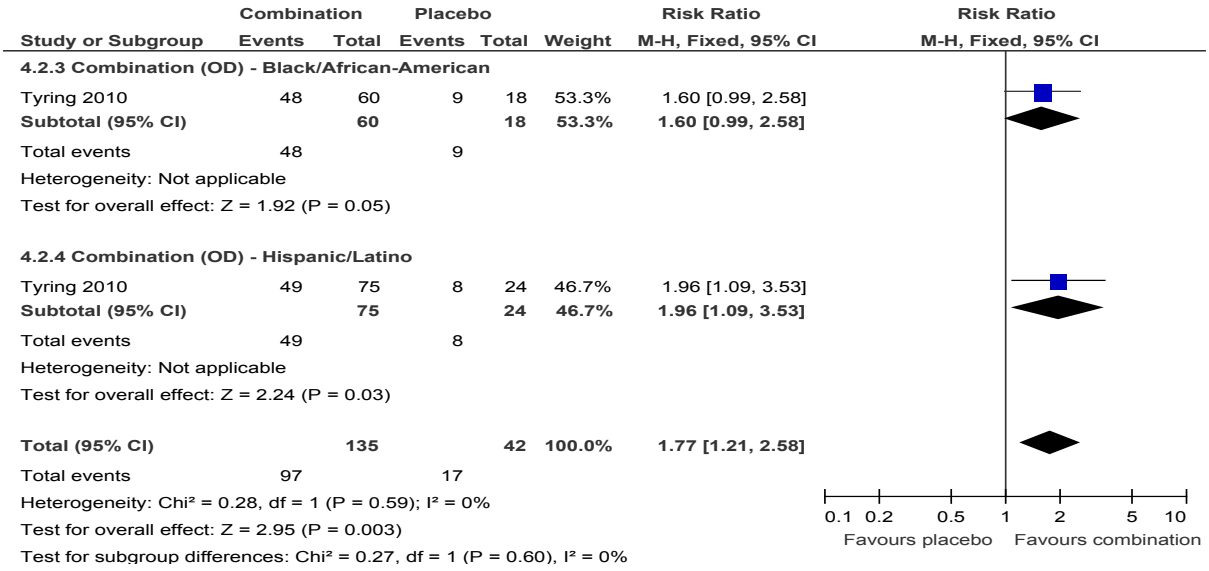


Figure 91: Patient's assessment (clear/nearly clear) at 8 weeks

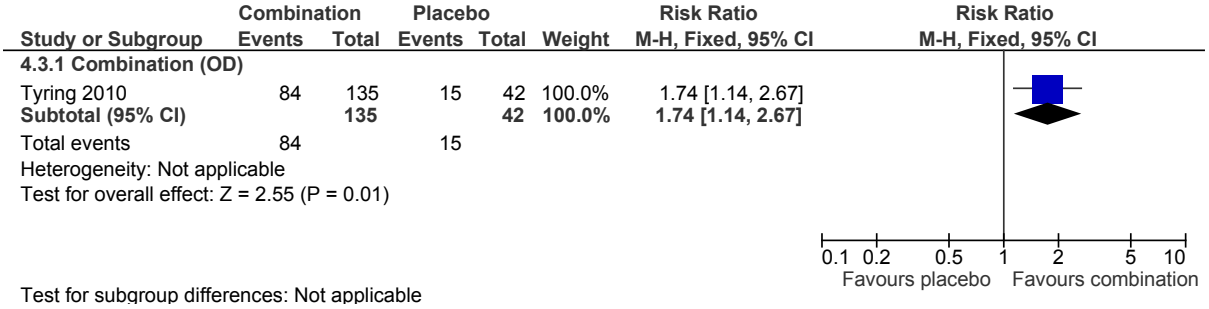
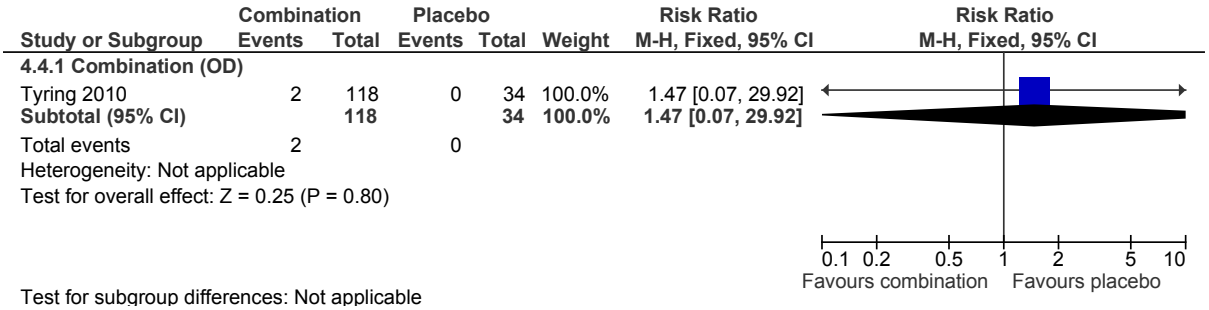
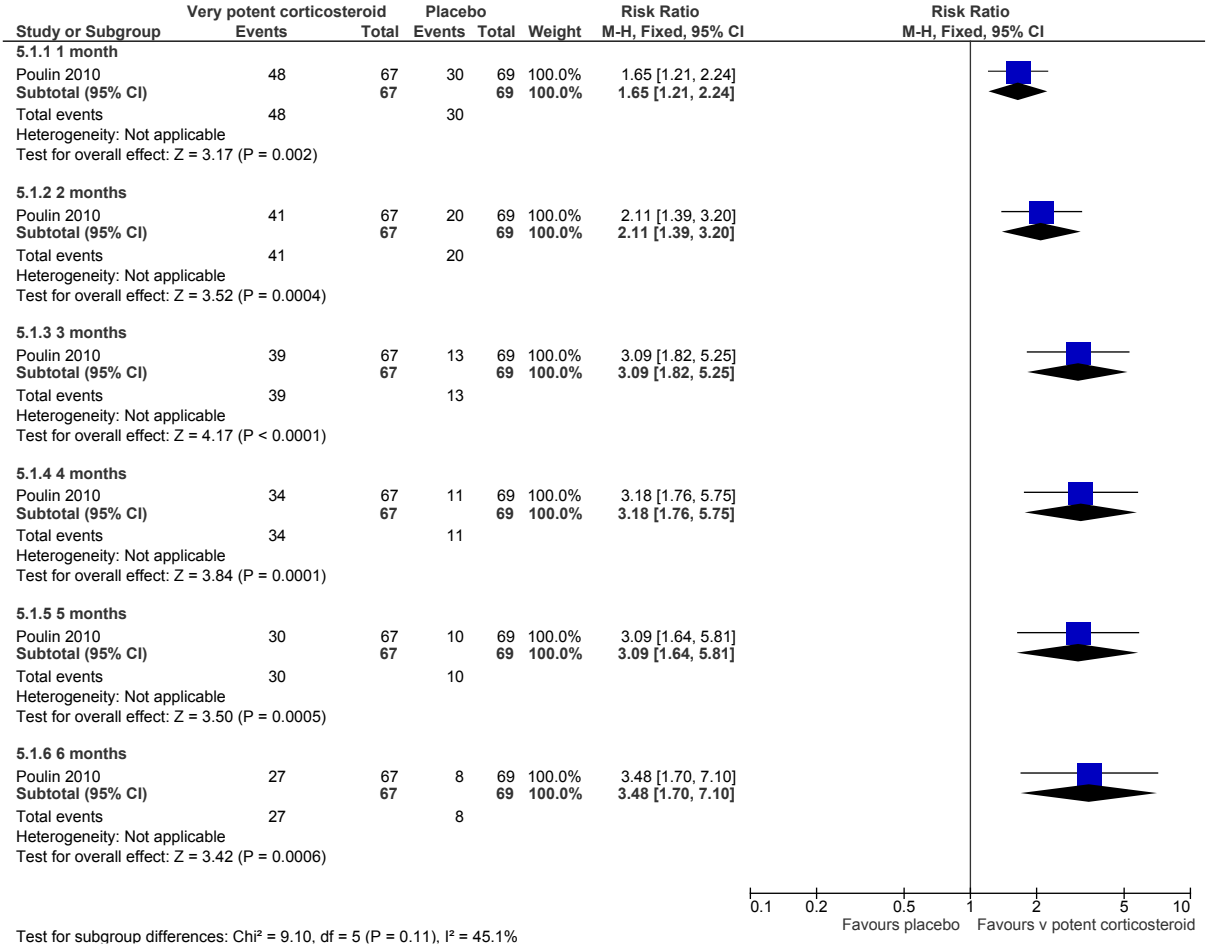


Figure 92: Withdrawal due to adverse events at 8 weeks



J.3.5 Scalp: Very potent corticosteroid vs placebo for maintenance of remission

Figure 93: Duration of remission (N still in remission)



Test for subgroup differences: Chi² = 9.10, df = 5 (P = 0.11), I² = 45.1%

Figure 94: Skin atrophy at 6 months

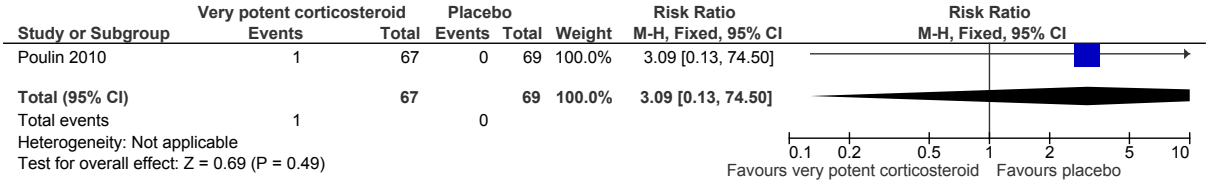
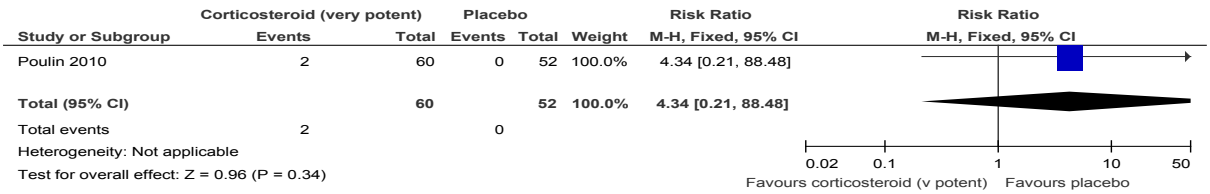


Figure 95: Withdrawals due to adverse events at 6 months

Note: different scale



J.3.6 Scalp: Vitamin D or vitamin D analogue vs potent corticosteroid

Figure 96: Investigator's assessment (clear/nearly clear) at 4-8 weeks

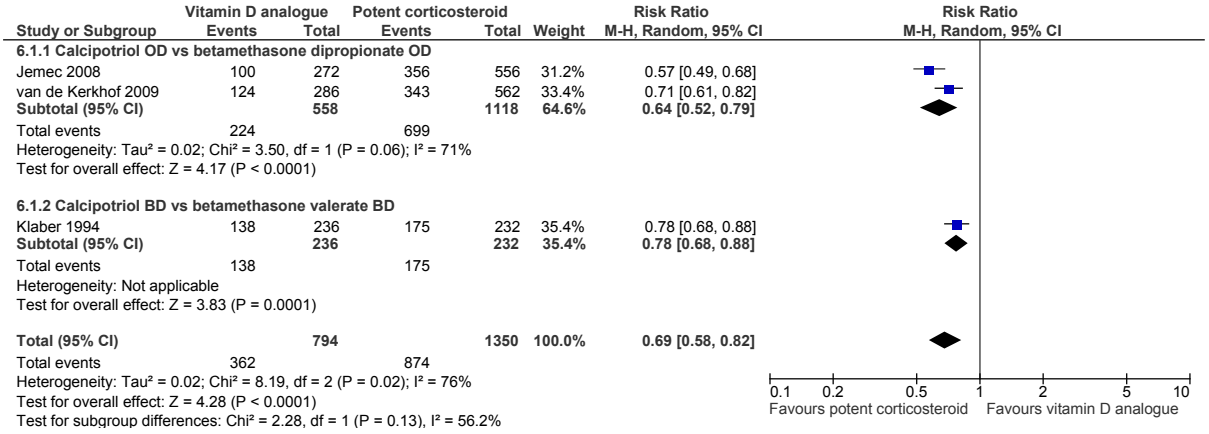


Figure 97: Patient's assessment (clear/nearly clear) at 4-8 weeks

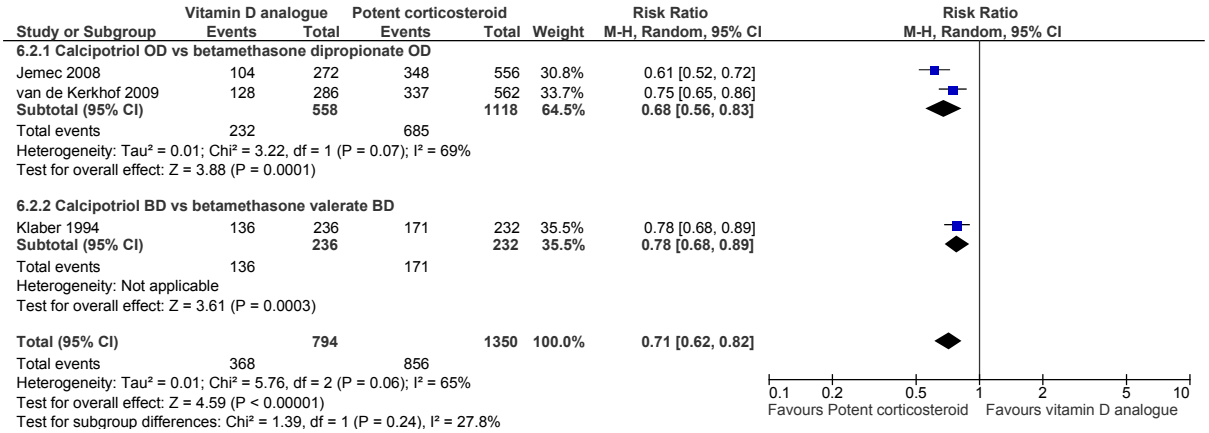


Figure 98: Relapse rate after 4 weeks

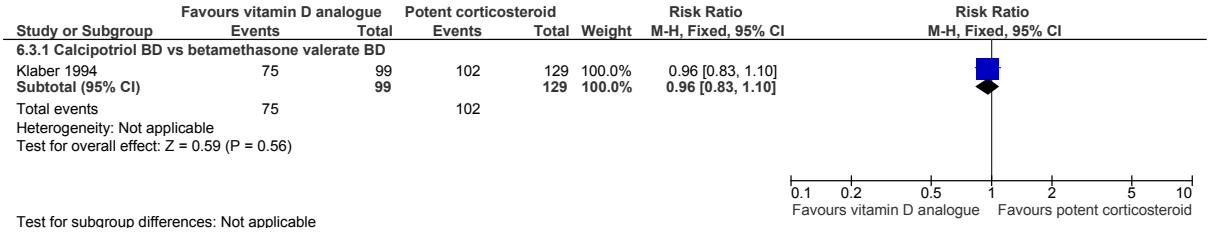


Figure 99: Withdrawal due to adverse events at 4-8 weeks

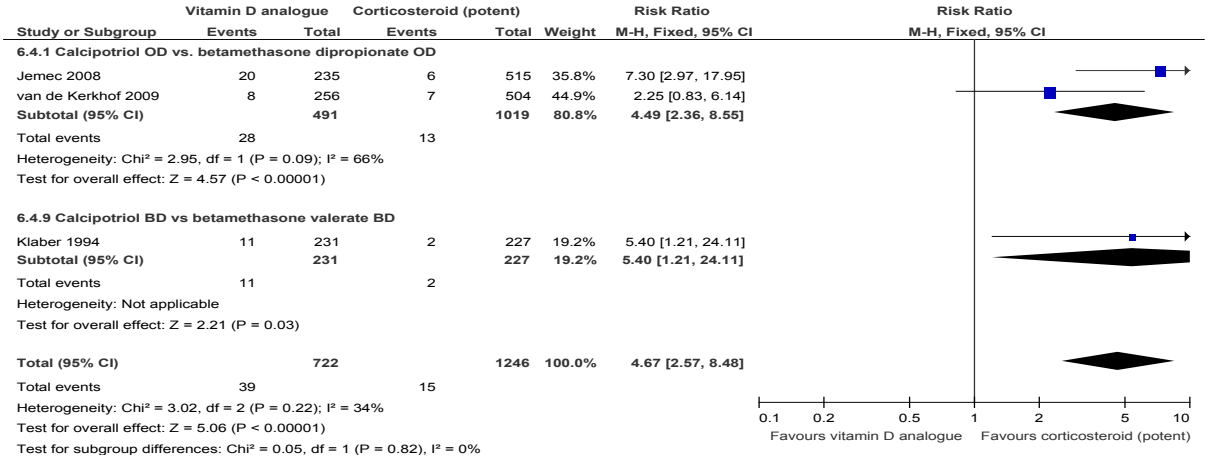
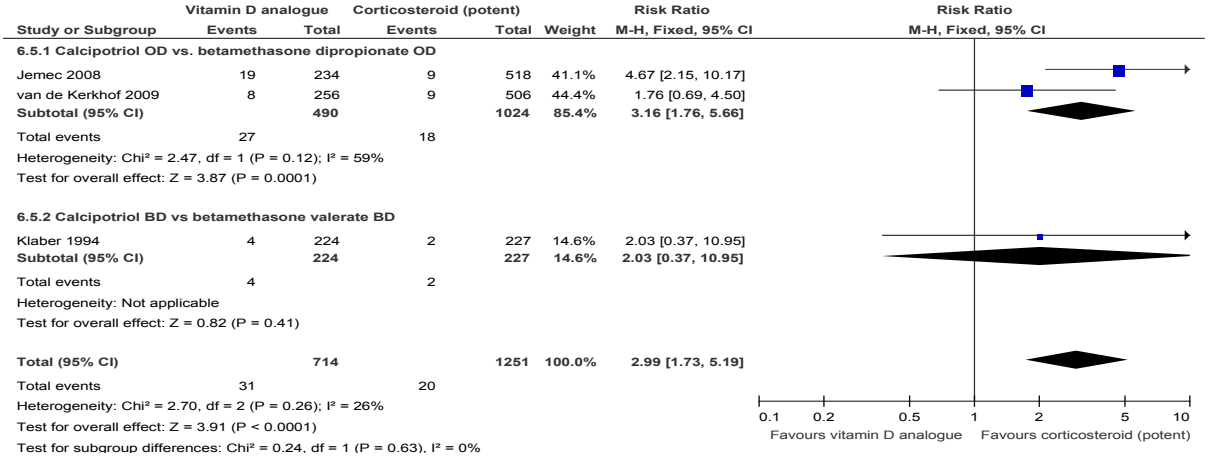


Figure 100: Withdrawal due to lack of effiacy at 4-8 weeks



J.3.7 Scalp: Vitamin D or vitamin D analogue vs very potent corticosteroid

Figure 101: Investigator's assessment (clear/nearly clear) at 4 weeks

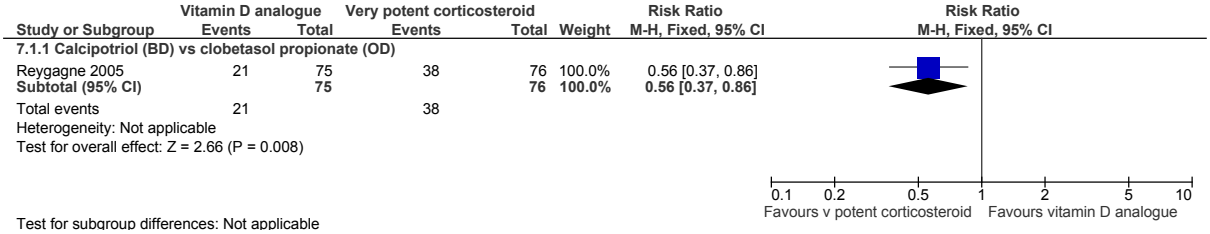


Figure 102: Patient's assessment (clear/nearly clear) at 4 weeks

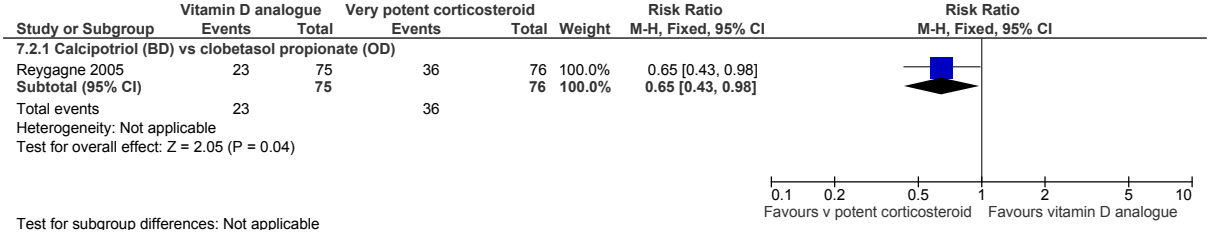


Figure 103: Skin atrophy at 4 weeks

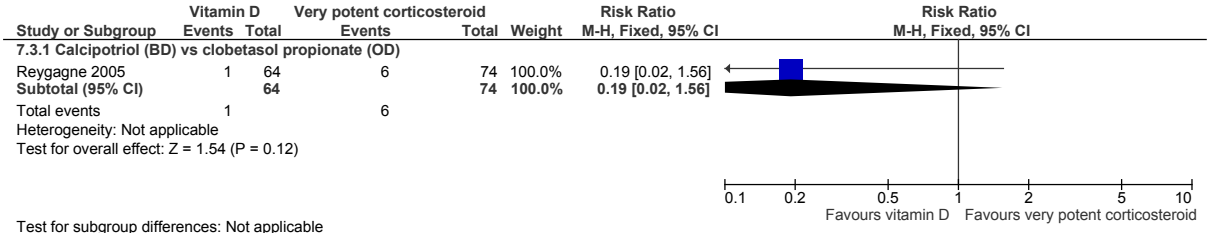
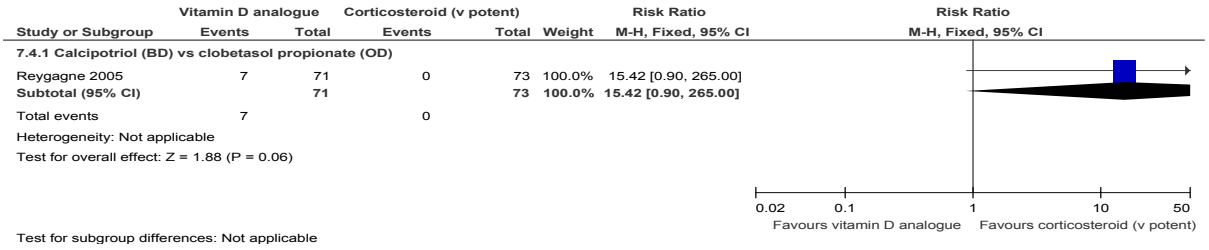


Figure 104: Withdrawal due to adverse events at 4 weeks

Note: different scale



J.3.8 Scalp: Combined product containing vitamin D analogue and potent corticosteroid vs potent corticosteroid

Figure 105: Investigator's assessment (clear/nearly clear) at 8 weeks

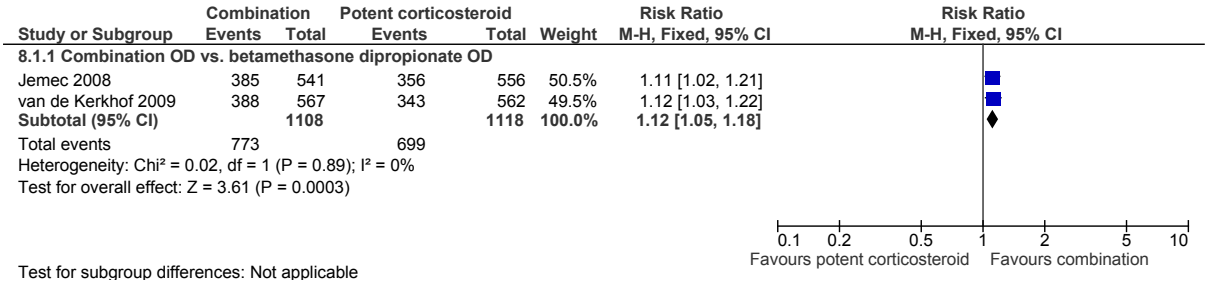


Figure 106: Patient's assessment (clear/nearly clear) at 8 weeks

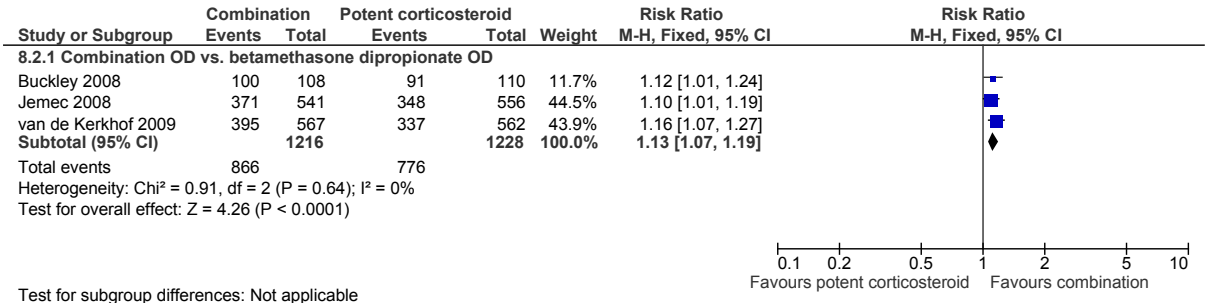


Figure 107: Withdrawal due to adverse events at 8 weeks

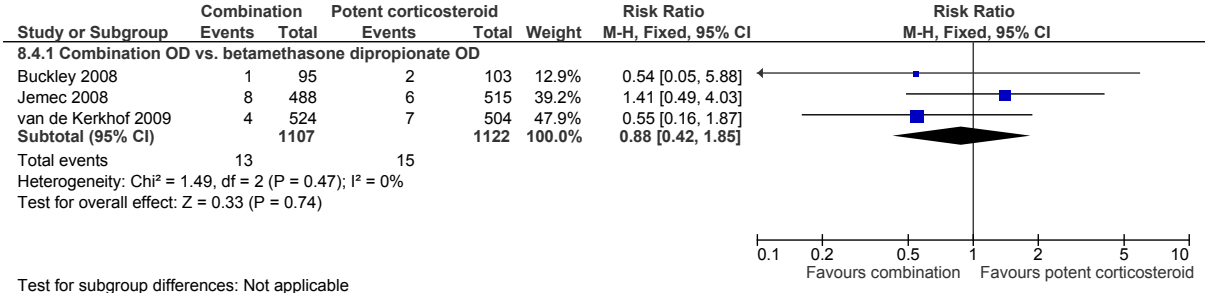
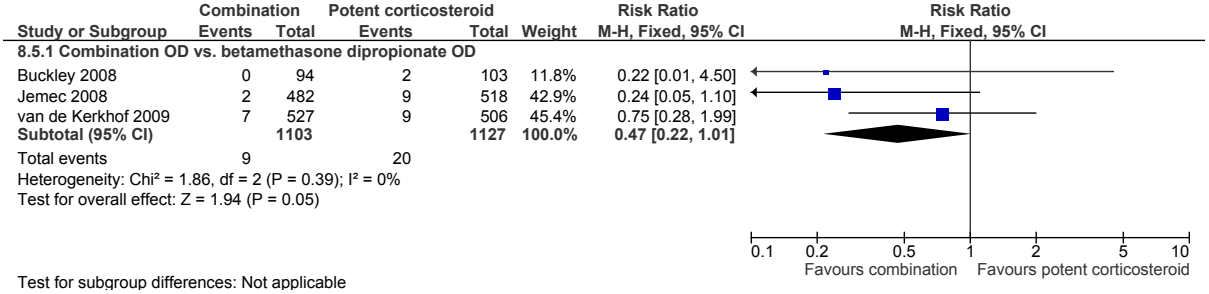


Figure 108: Withdrawal due to lack of effiacy at 8 weeks



J.3.9 Scalp: Combined product containing potent corticosteroid and vitamin D analogue vs vitamin D or vitamin D analogue

Figure 109: Investigator's assessment (clear/nearly clear) at 8 weeks

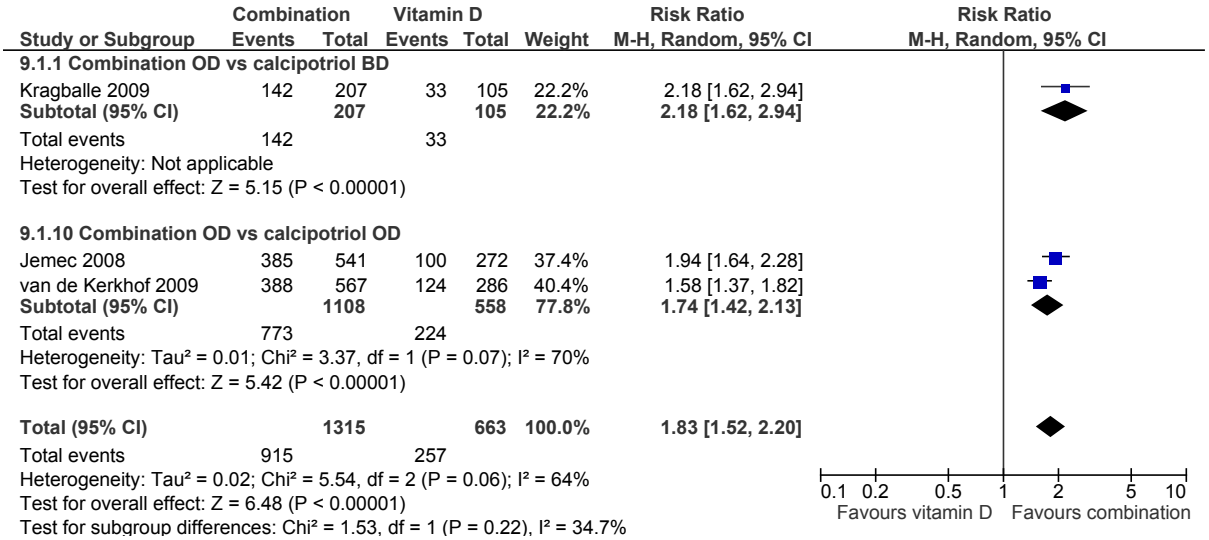


Figure 110: Patient's assessment (clear/nearly clear) at 8 weeks

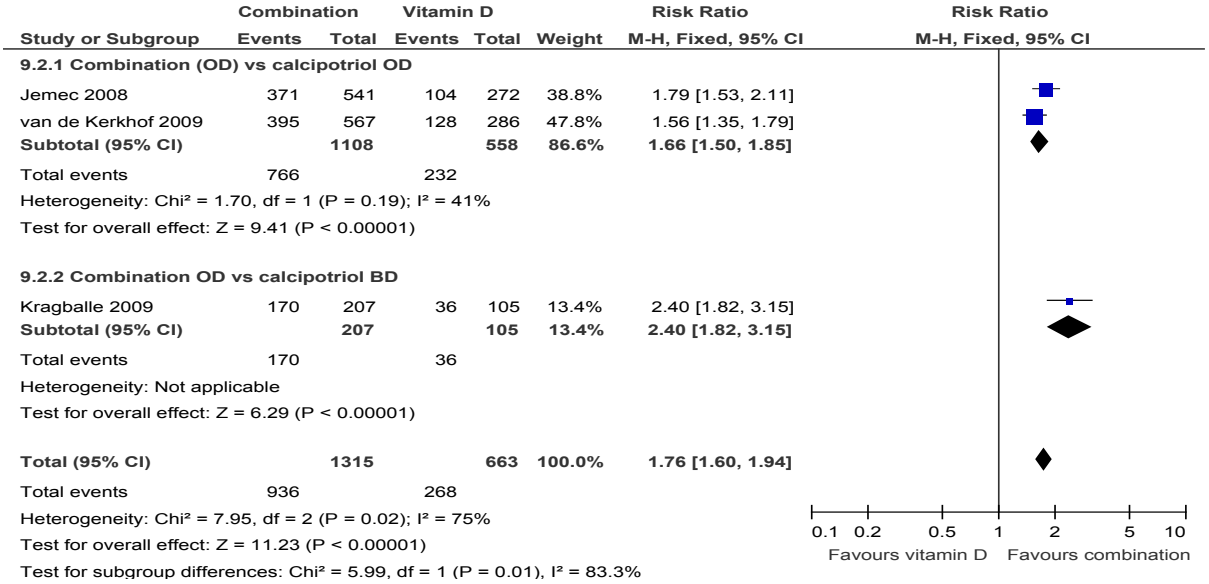


Figure 111: Relapse rate at 8 weeks

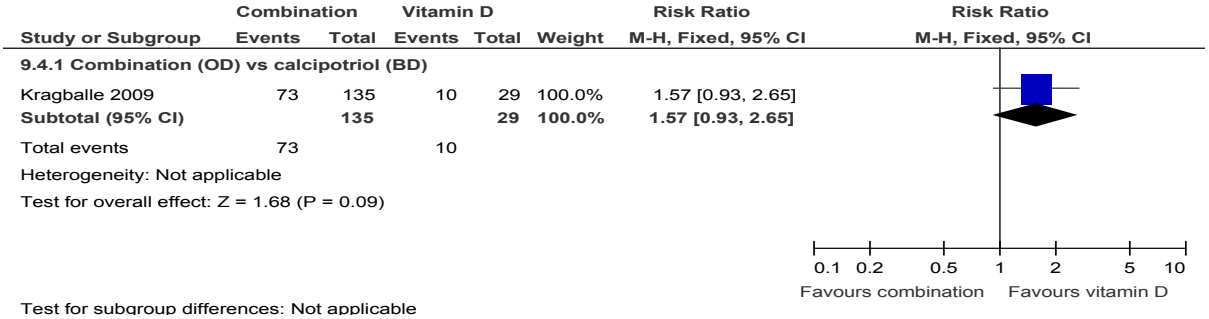


Figure 112: Withdrawal due to adverse events at 8 weeks

Note: different scale

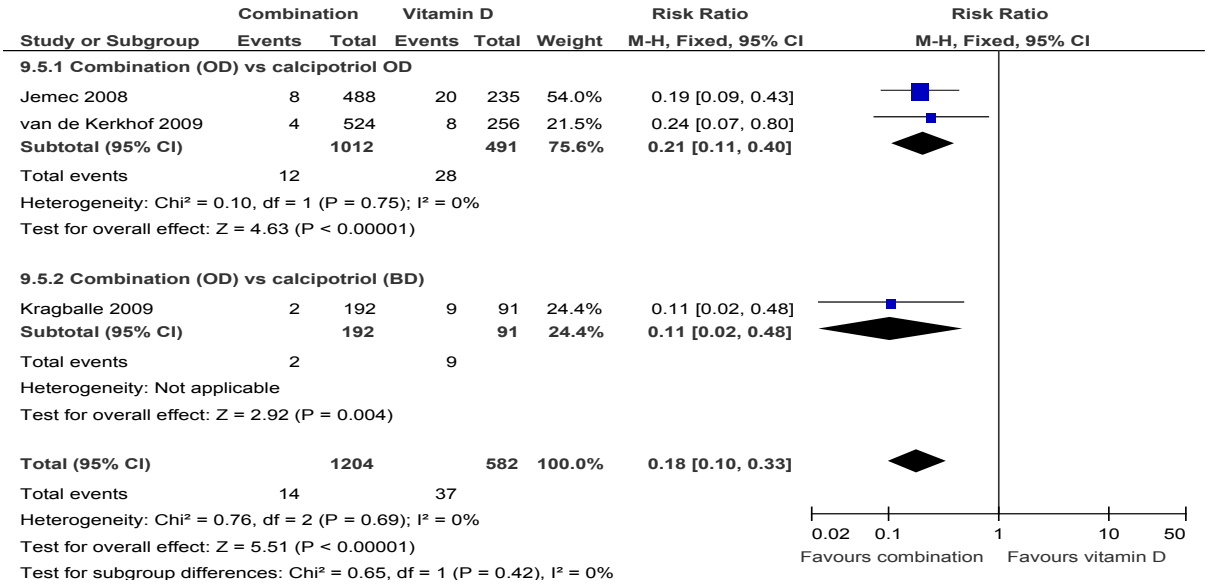


Figure 113: Withdrawal due to adverse events at 52 weeks

Figure 114: Withdrawal due to treatment failure at 8 weeks

Note: different scale

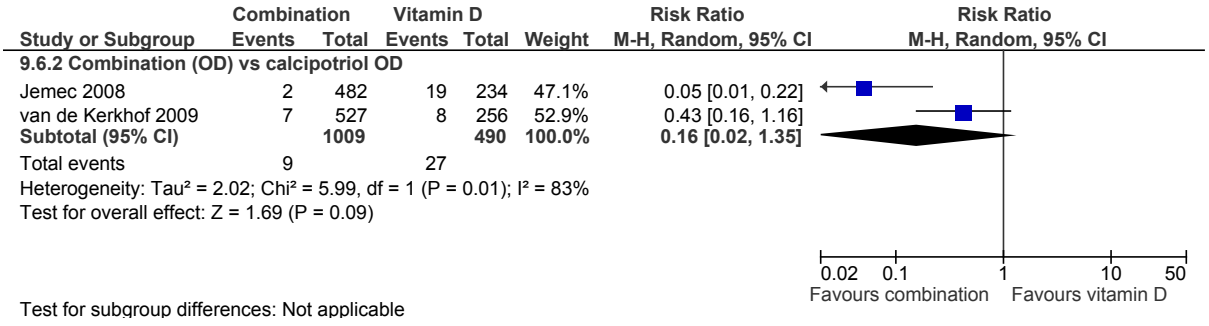
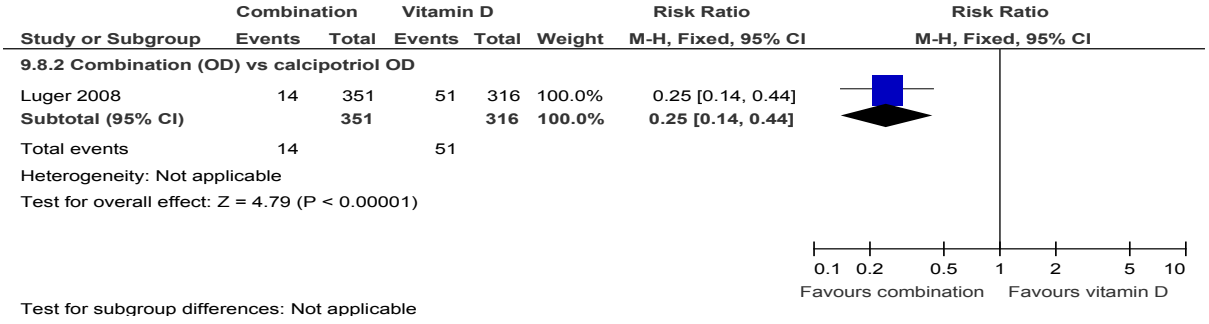
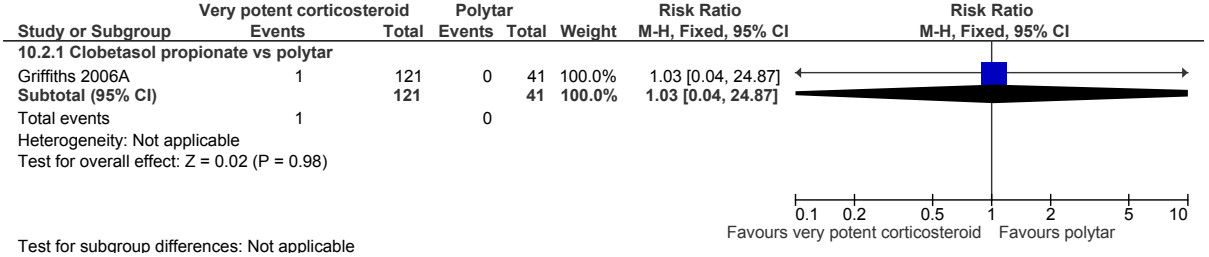


Figure 115: Withdrawal due to treatment failure at 52 weeks



J.3.10 Scalp: Very potent corticosteroid vs coal tar polytherapy

Figure 116: Withdrawal due to adverse events at 4 weeks



J.3.11 Scalp: Vitamin D or vitamin D analogue vs coal tar polytherapy

Figure 117: Investigator's assessment (at least moderate improvement) at 8 weeks

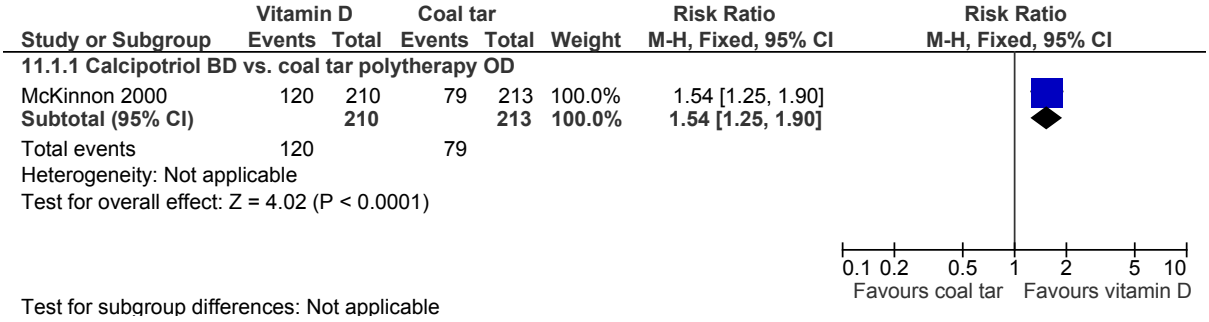
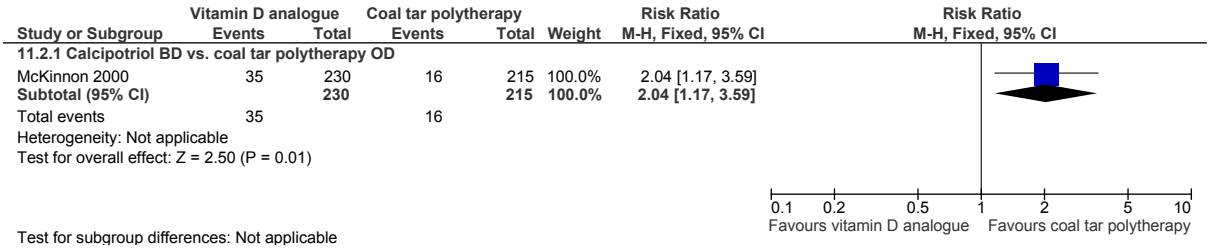


Figure 118: Withdrawals due to adverse events at 8 weeks



J.3.12 Face and flexures: Tacrolimus vs placebo

Figure 119: Investigator's assessment (clear/nearly clear) at 8 weeks

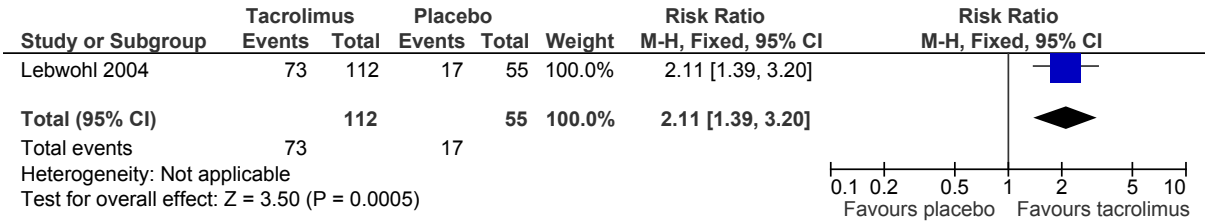


Figure 120: Withdrawal due to adverse events at 8 weeks

Note: different scale

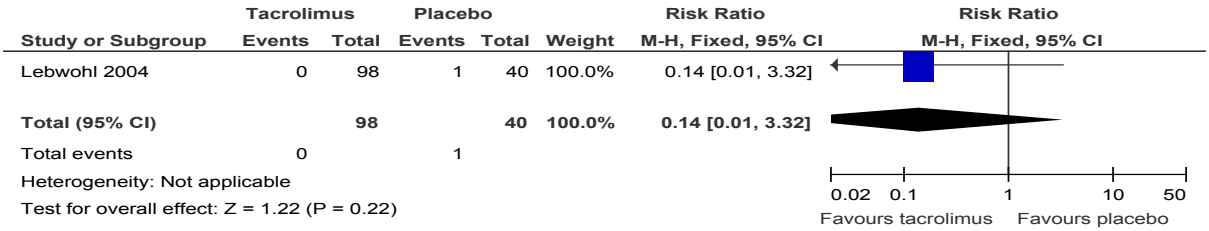
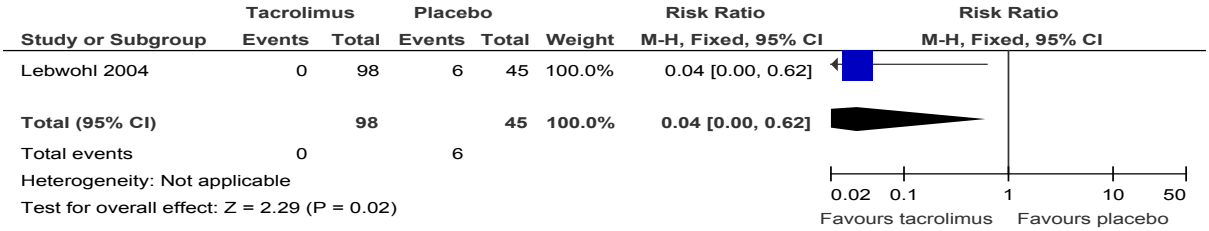


Figure 121: Withdrawal due to lack of efficacy at 8 weeks

Note: different scale



J.3.13 Face and flexures: pimecrolimus vs placebo

Figure 122: Investigator's assessment (clear/nearly clear) at 8 weeks

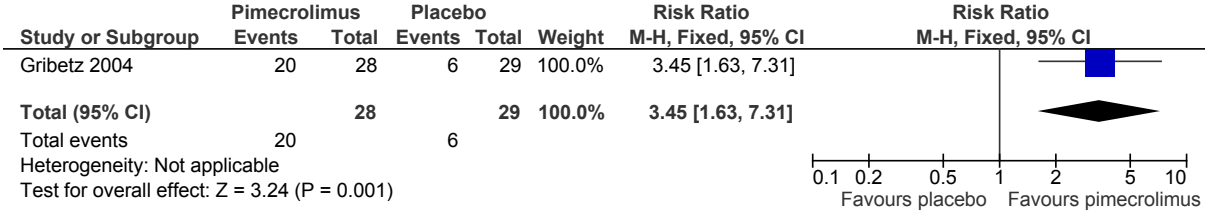
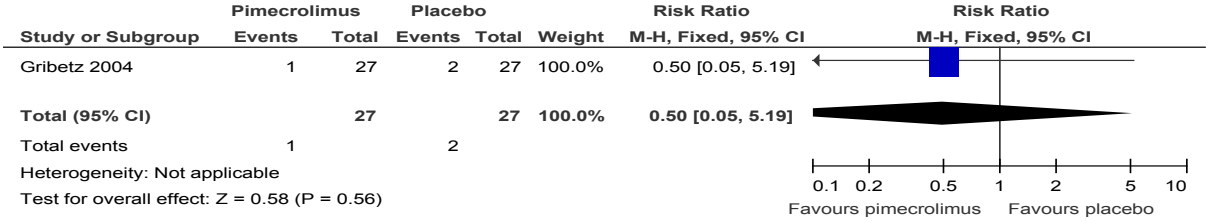
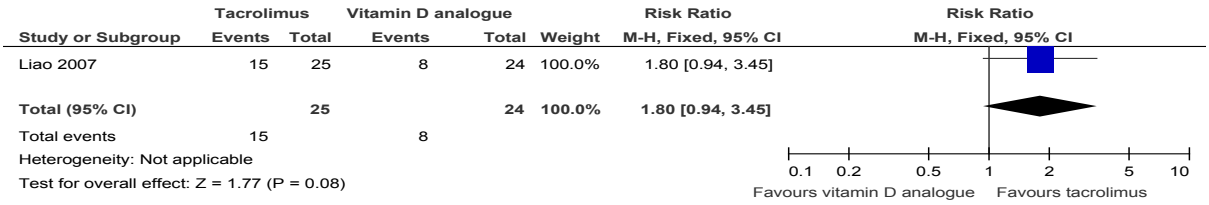


Figure 123: Withdrawal due to lack of efficacy at 8 weeks



J.3.14 Face and flexures: tacrolimus vs vitamin D or vitamin D analogue

Figure 124: Investigator's assessment (clear/nearly clear) at 6 weeks



J.4 Phototherapy

J.4.1 Broadband vs narrowband UVB

Figure 125: Clear at the end of treatment

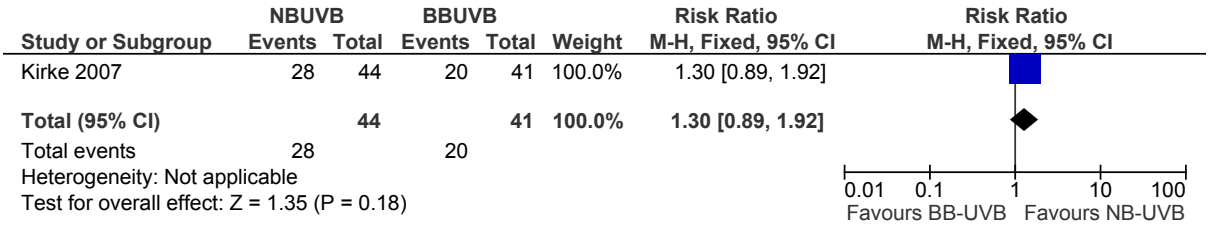


Figure 126: Clear at 3 months post-treatment

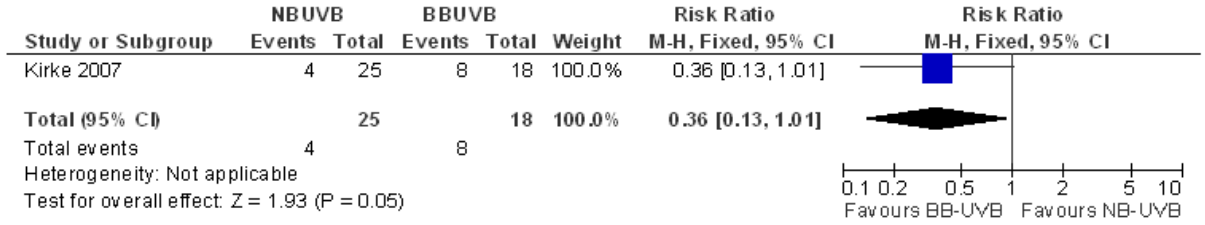


Figure 127: Clear at 6 months post-treatment

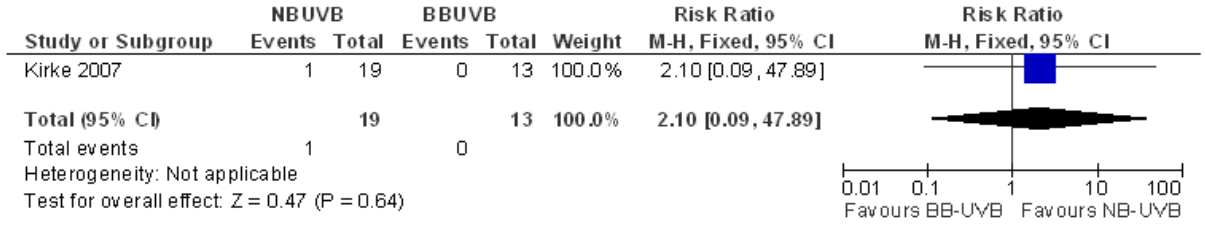
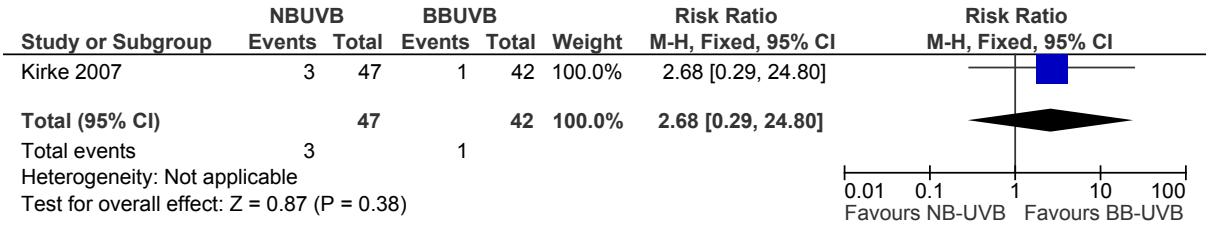


Figure 128: Withdrawal due to toxicity



J.4.2 Narrowband vs PUVA

1.1.1.1 Oral PUVA (between patient randomisation)

Figure 129: Clear/nearly clear on PGA at end of treatment (maximum 30-40 exposures)

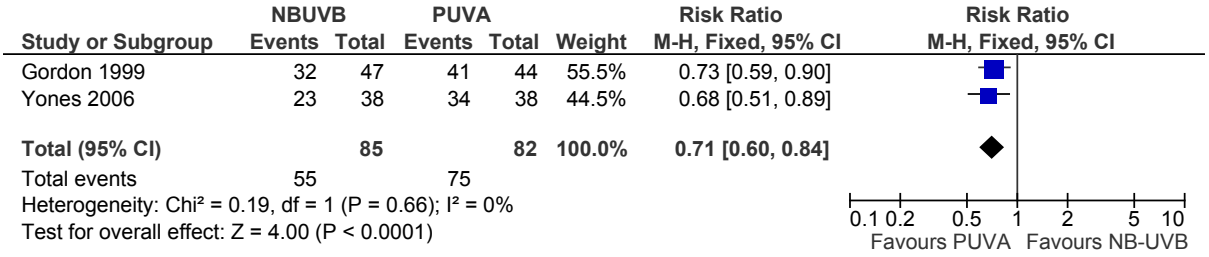


Figure 130: Clear/nearly clear on PGA at end of treatment (maximum 30 exposures; post-hoc skin type subgroup analysis)

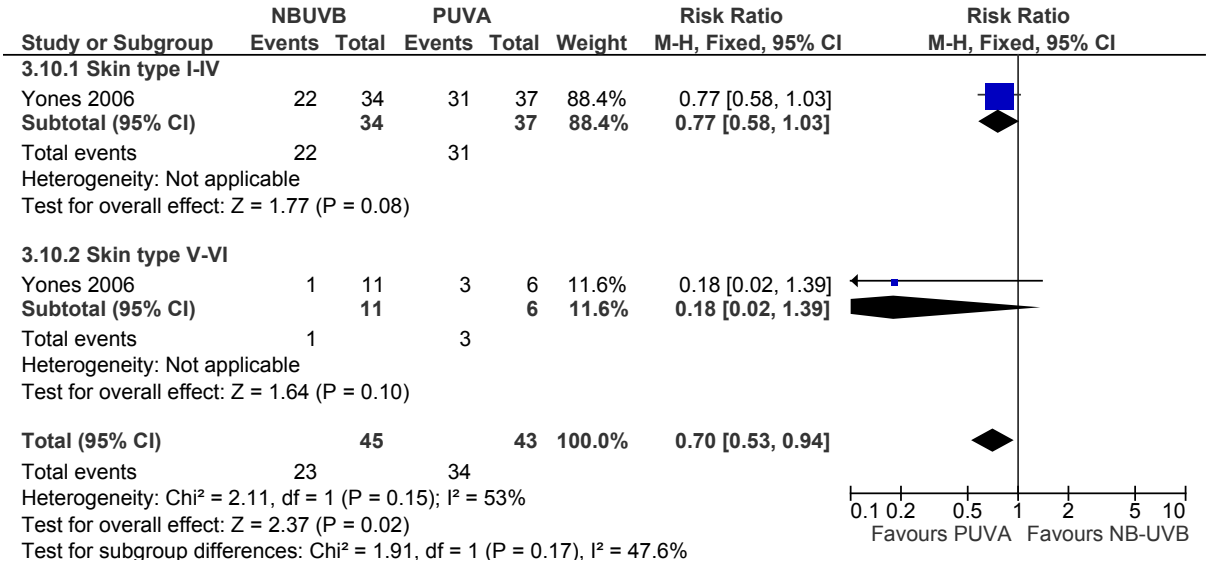


Figure 131: Mean time to PASI75 (weeks) after maximum follow-up of 4 months

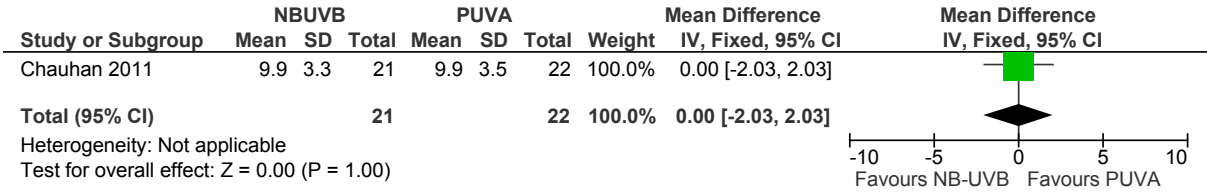


Figure 132: Mean time to clearance (days) after maximum follow-up of 3 months

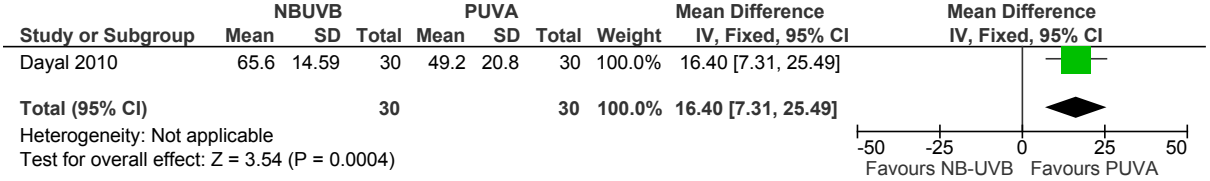


Figure 133: PASI75 at 3-4 months or a maximum of 20 treatments

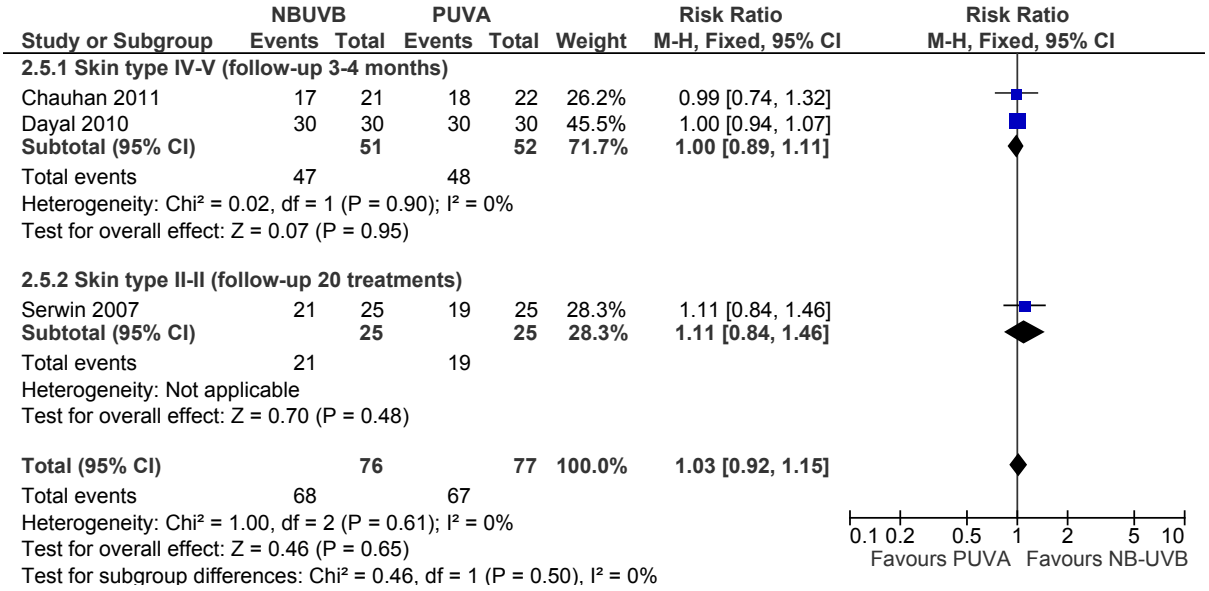


Figure 134: Final PASI after up to 20 treatments

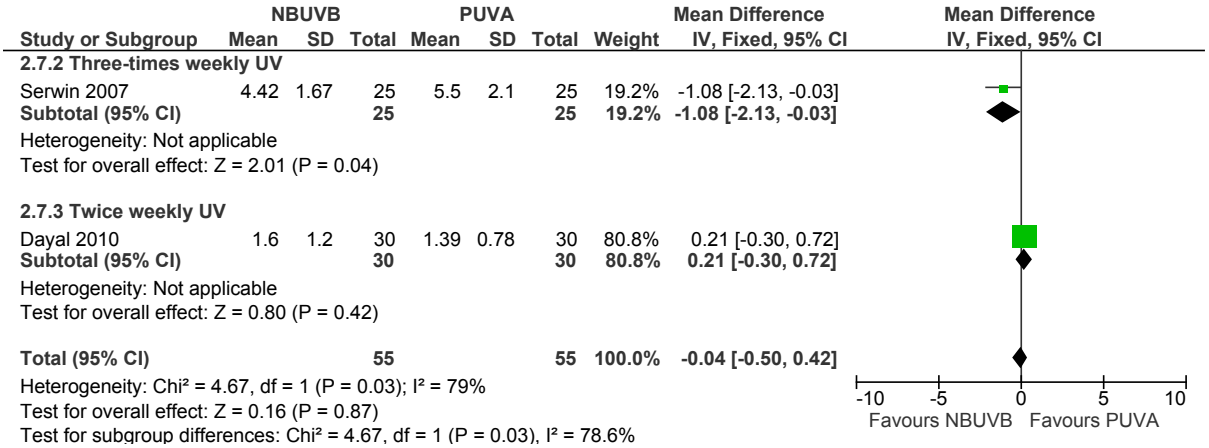


Figure 135: Relapse rate for clearers (6 or 12 months post-treatment)

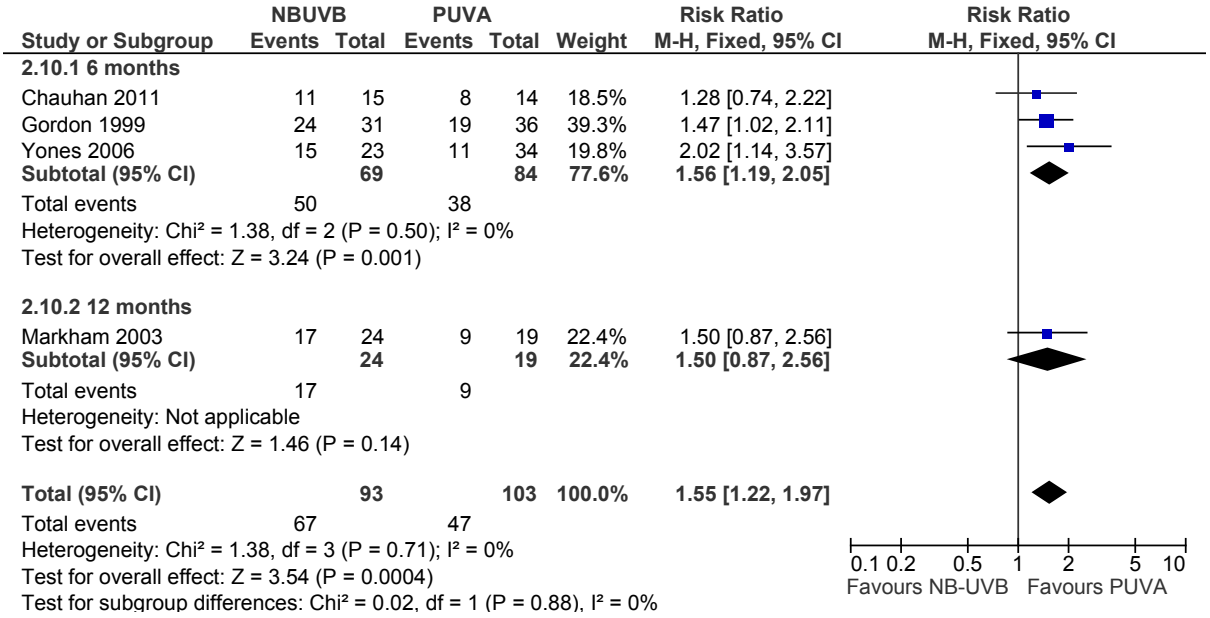
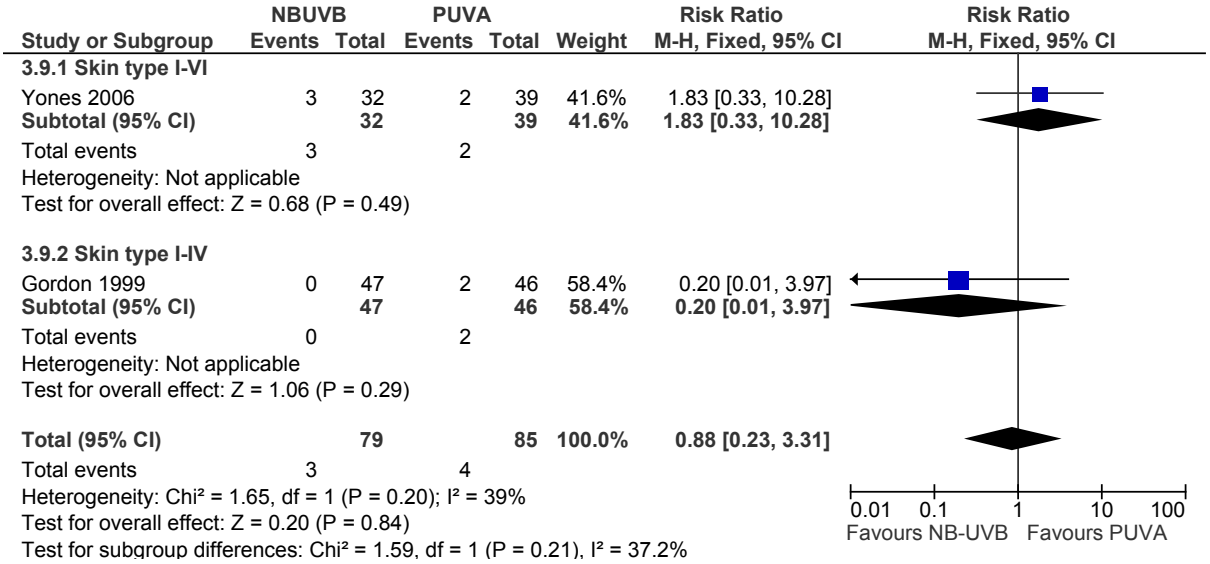


Figure 136: Withdrawal due to toxicity after a maximum of 30-40 treatments



J.4.3 Bath PUVA (within patient randomisation)

Figure 137: Time-to-remission (clearance or minimal residual activity) after a maximum of 30 treatments

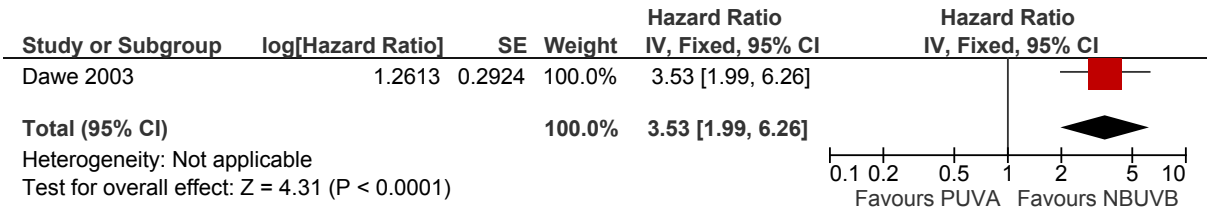


Figure 138: Mean change in PASI at 10 weeks

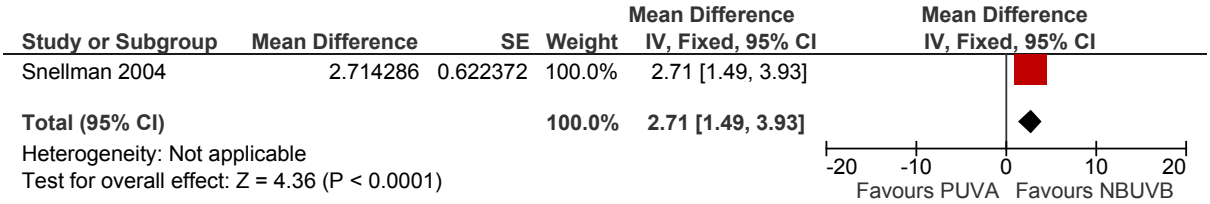


Figure 139: Mean time to relapse (days) after a maximum of 30 exposures

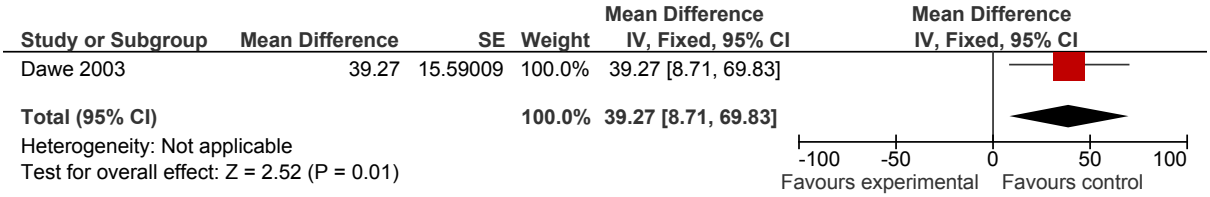


Figure 140: Withdrawal due to toxicity at 10 weeks

Note different scale

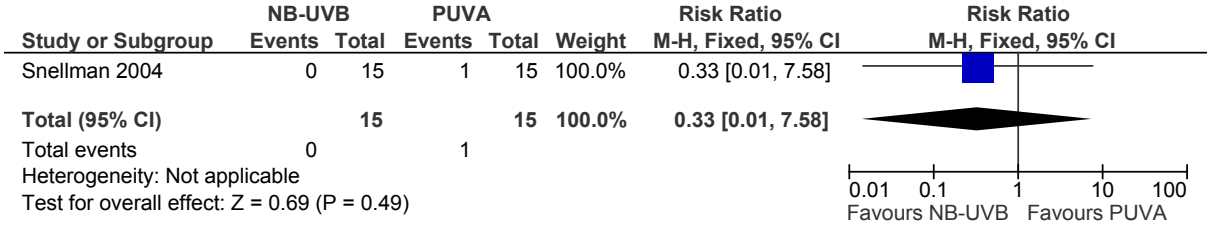
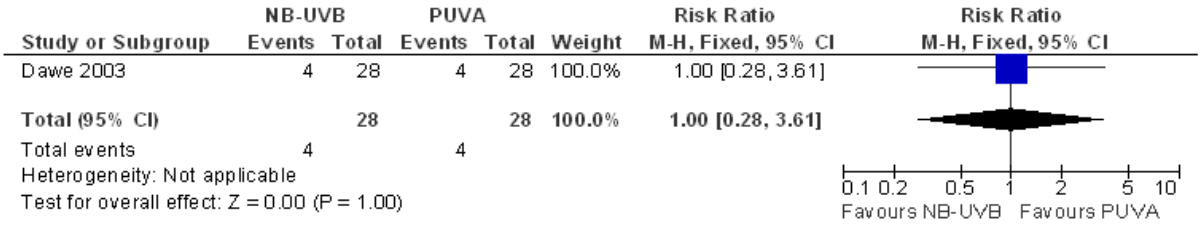
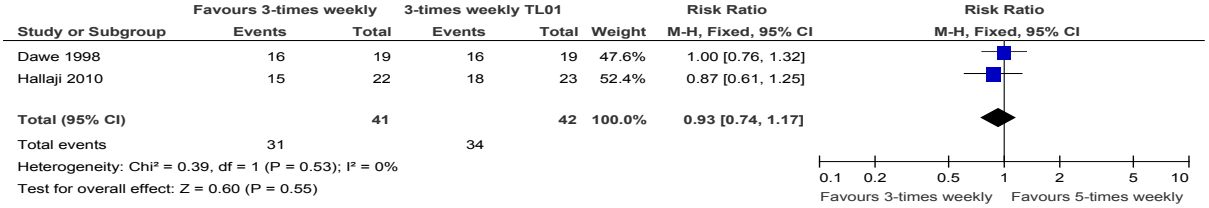


Figure 141: Burn after maximum of 30 treatments



J.4.4 NBUVB five-times vs three-times weekly

Figure 142: Clearance at 4.7-23 weeks or a maximum of 30 treatments



J.4.5 NBUVB two-times vs three-times weekly

Between patient

Figure 143: Clearance

Study or Subgroup	TL01 twice weekly Events	Total	TL01 three-times weekly Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cameron 2002	40	44	44	48	100.0%	0.99 [0.87, 1.13]
Total (95% CI)		**44**		**48**	**100.0%**	**0.99 [0.87, 1.13]**
Total events	40		44			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)

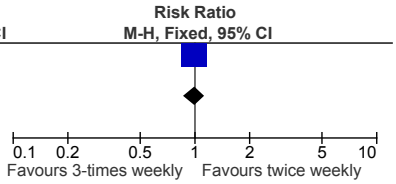


Figure 144: Withdrawal due to toxicity

Note different scale

Study or Subgroup	TL01 twice weekly Events	Total	TL01 three-times weekly Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cameron 2002	2	42	1	45	100.0%	2.14 [0.20, 22.77]
Total (95% CI)		**42**		**45**	**100.0%**	**2.14 [0.20, 22.77]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

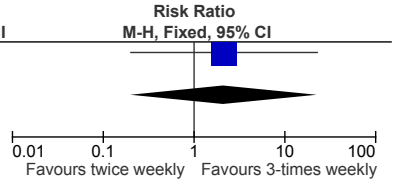
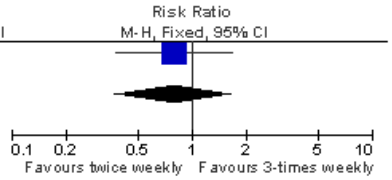


Figure 145: Burn

Study or Subgroup	TL01 twice weekly Events	Total	TL01 three-times weekly Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cameron 2002	10	58	12	55	100.0%	0.79 [0.37, 1.68]
Total (95% CI)		58		55	100.0%	0.79 [0.37, 1.68]
Total events	10		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)



J.4.6 Oral PUVA three-times vs two-times weekly

Within and between patient

Figure 146: Clear/nearly clear on IAGI at 12 weeks

Study or Subgroup	PUVA three-times weekly Events	Total	PUVA twice weekly Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Mofty 2008	4	9	9	10	100.0%	0.49 [0.23, 1.05]
Total (95% CI)		9		10	100.0%	0.49 [0.23, 1.05]
Total events	4		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)

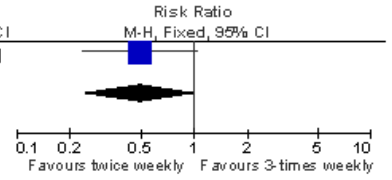


Figure 147: Percentage change in PASI at 12 weeks

Study or Subgroup	PUVA three-times weekly Mean	SD	Total	PUVA twice weekly Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
El-Mofty 2008	66.88	29.31	9	82.31	18.22	10	100.0%	-15.43 [-37.66, 6.80]
Total (95% CI)			9			10	100.0%	-15.43 [-37.66, 6.80]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)

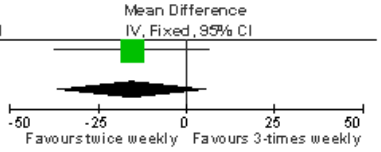
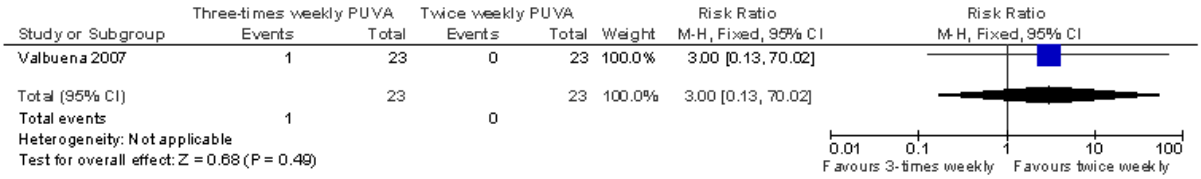


Figure 148: Burn after a maximum of 25 treatments

Note different scale



J.4.7 Oral hand and foot PUVA vs no treatment for palmoplantar pustulosis

Figure 149: Clearance at 7.5-12 weeks

Note different scale

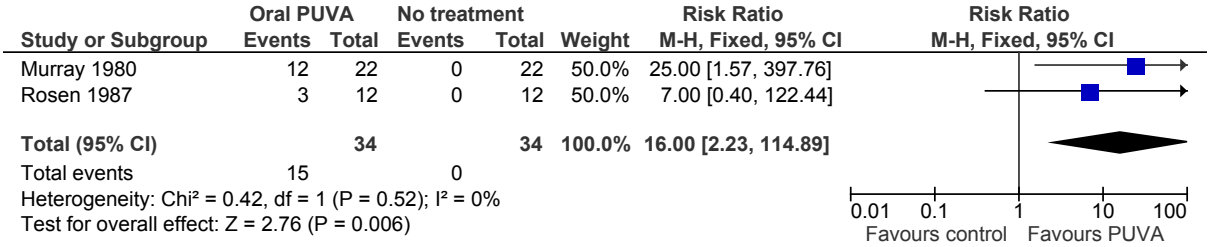


Figure 150: Improved at 7.5-12 weeks

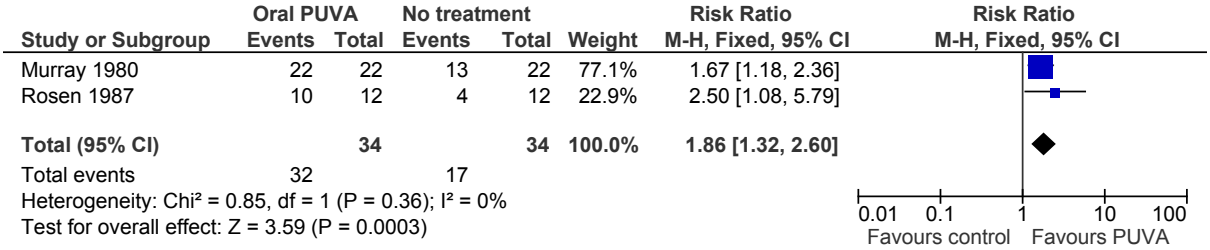


Figure 151: Withdrawal due to toxicity at 7.5-12 weeks

Note different scale

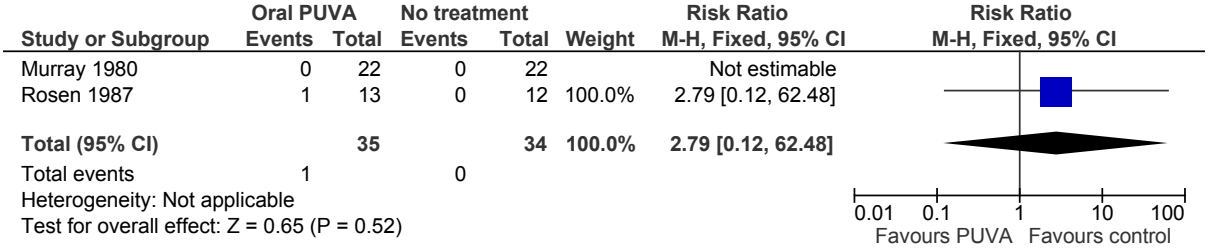
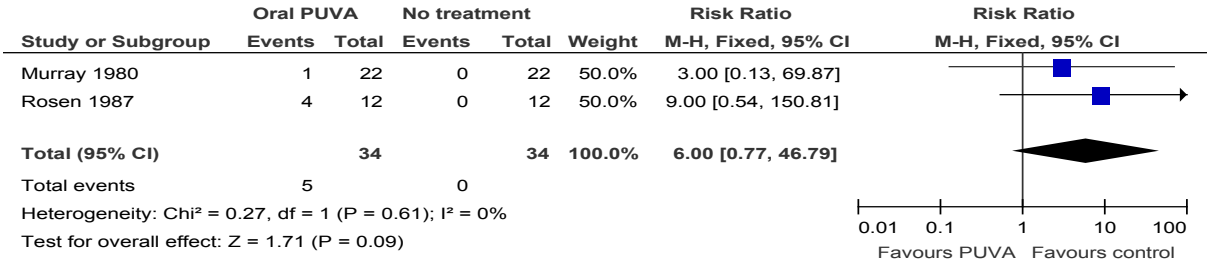


Figure 152: Burn at 7.5-12 weeks

Note different scale



J.4.8 Cream hand and foot PUVA vs NBUVB for palmoplantar pustulosis

Figure 153: Clear/nearly clear on IAGI at 9 weeks

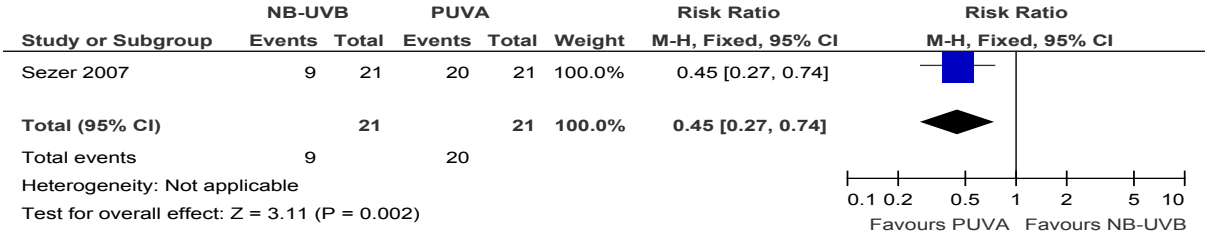


Figure 154: Withdrawal due to toxicity at 9 weeks

Note different scale

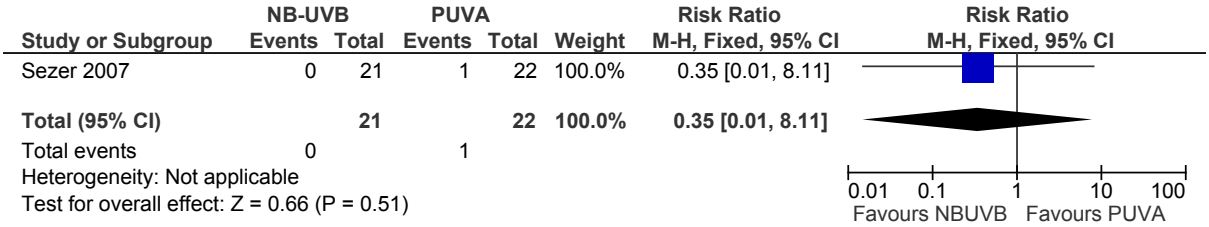
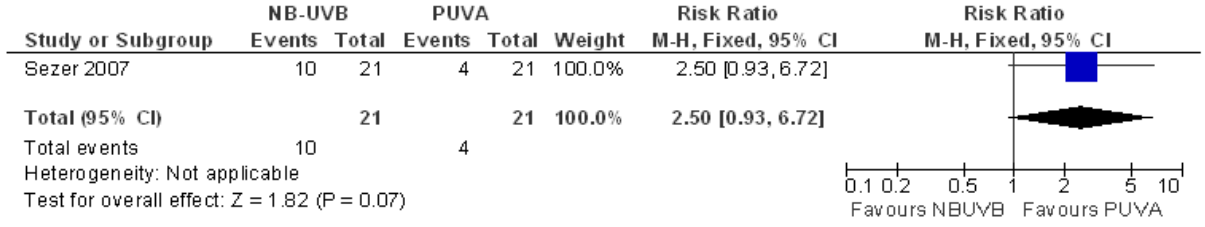


Figure 155: Relapse 10 weeks post-treatment



J.4.9 Home vs hospital UVB for psoriasis

Figure 156: Clear/nearly clear (PASI90) at a maximum of 46 treatments

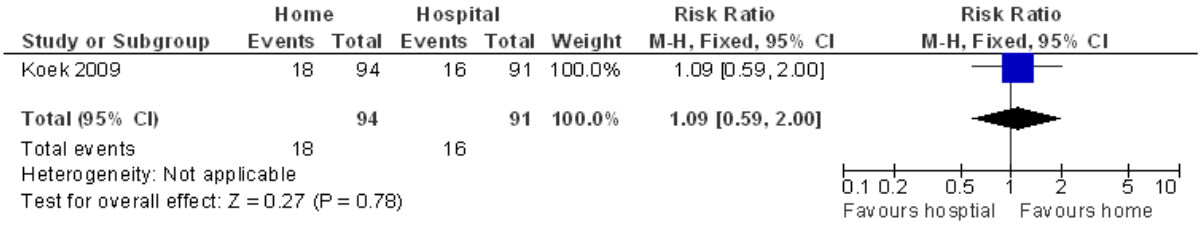


Figure 157: PASI75 at a maximum of 46 treatments

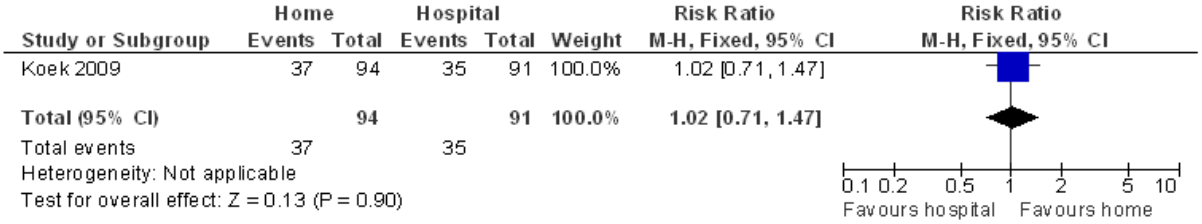
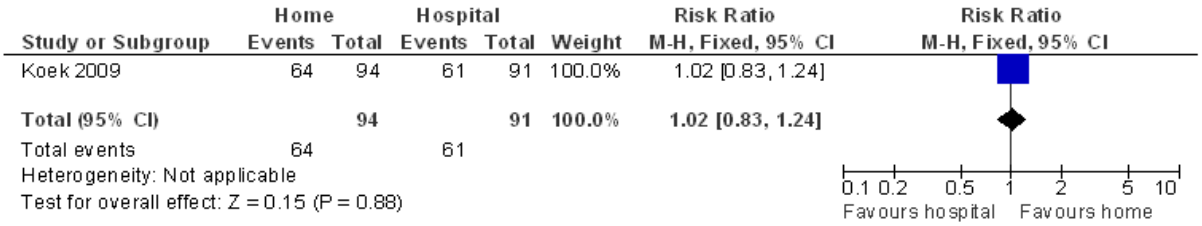


Figure 158: PASI50 at a maximum of 46 treatments



J.5 Phototherapy combined with acitretin

J.5.1 Acitretin vs acitretin plus BBUVB

Figure 159: Clear/nearly clear on IAGI at a maximum of 30 treatments

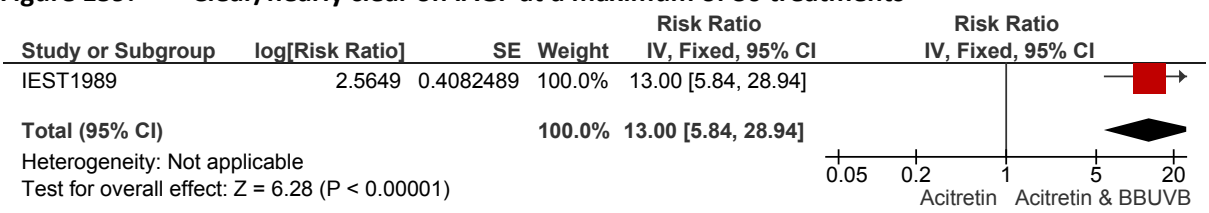
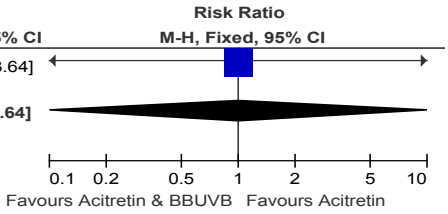


Figure 160: Withdrawal due to drug toxicity at a maximum of 30 treatments

Study or Subgroup	Acitretin Events	Total	Acitretin & BBUVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
IEST1989	1	9	1	9	100.0%	1.00 [0.07, 13.64]
Total (95% CI)		**9**		**9**	**100.0%**	**1.00 [0.07, 13.64]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



J.5.2 Acitretin plus BBUVB vs Placebo plus BBUVB

Figure 161: Clear/nearly clear on IAGI at 8 weeks

Study or Subgroup	Acitretin & BBUVB Events	Total	Placebo & BBUVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RUZICKA1990	16	40	6	38	100.0%	2.53 [1.11, 5.79]
Total (95% CI)		**40**		**38**	**100.0%**	**2.53 [1.11, 5.79]**
Total events	16		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)

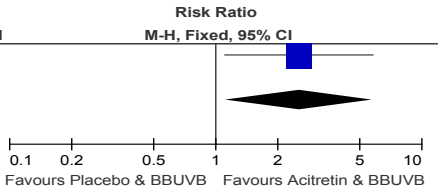
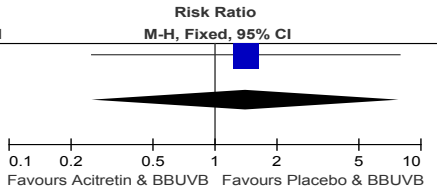


Figure 162: Withdrawal due to drug toxicity at 8 weeks

Study or Subgroup	Acitretin & BBUVB Events	Total	Placebo & BBUVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RUZICKA1990	3	34	2	32	100.0%	1.41 [0.25, 7.91]
Total (95% CI)		**34**		**32**	**100.0%**	**1.41 [0.25, 7.91]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)



J.5.3 Acitretin plus NBUVB versus Acitretin plus PUVA

Figure 163: PASI75 at 8 weeks

Study or Subgroup	Acitretin & TL-01 Events	Total	Acitretin & PUVA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
OZDEMIR2008	17	30	19	30	100.0%	0.89 [0.59, 1.35]
Total (95% CI)		**30**		**30**	**100.0%**	**0.89 [0.59, 1.35]**
Total events	17		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

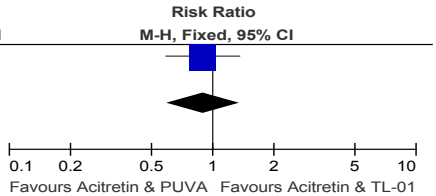


Figure 164: PASI50 at 8 weeks

Study or Subgroup	Acitretin & TL-01 Events	Total	Acitretin & PUVA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
OZDEMIR2008	21	30	23	30	100.0%	0.91 [0.67, 1.24]
Total (95% CI)		**30**		**30**	**100.0%**	**0.91 [0.67, 1.24]**
Total events	21		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

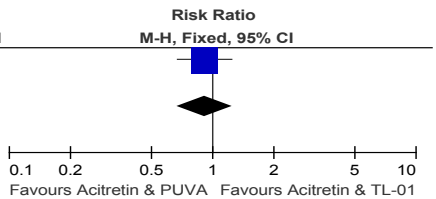


Figure 165: Number of UV treatments at 8 weeks

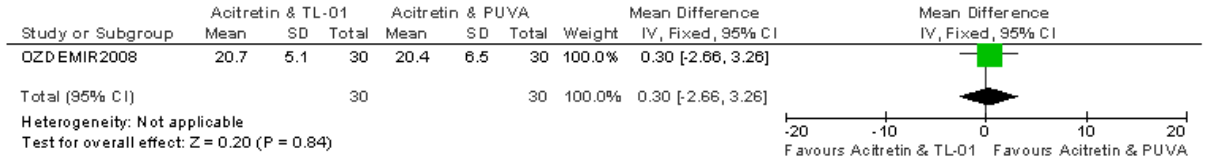


Figure 166: Maintenance of remission (at 3 months)

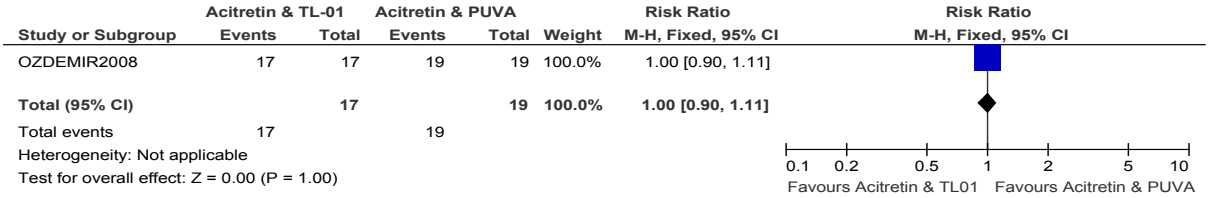


Figure 167: Burn at 8 weeks

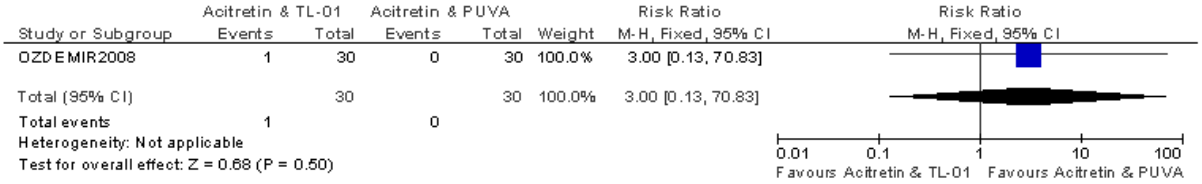
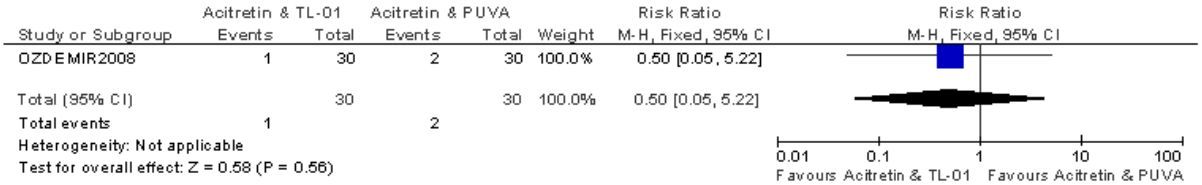


Figure 168: Withdrawal due to drug toxicity at 8 weeks



J.5.4 Acitretin plus PUVA vs Placebo plus PUVA

Figure 169: Clear or nearly clear on IAGI at 8-12 weeks

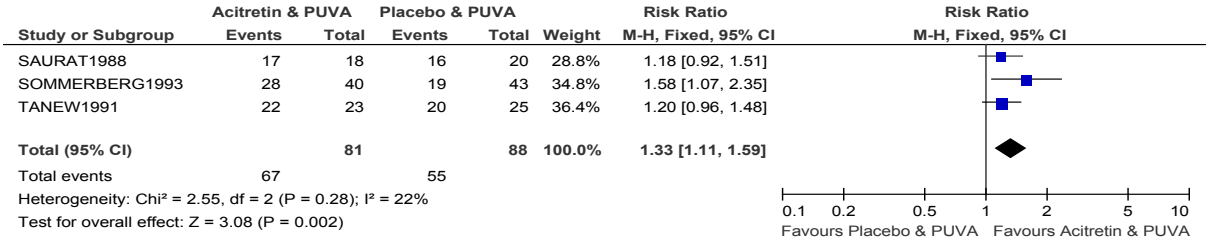


Figure 170: Time to remission after a maximum of 12 weeks

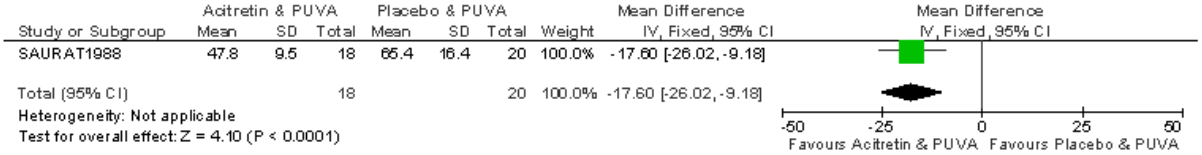


Figure 171: Mean number of UVA treatments after a maximum of 8 weeks

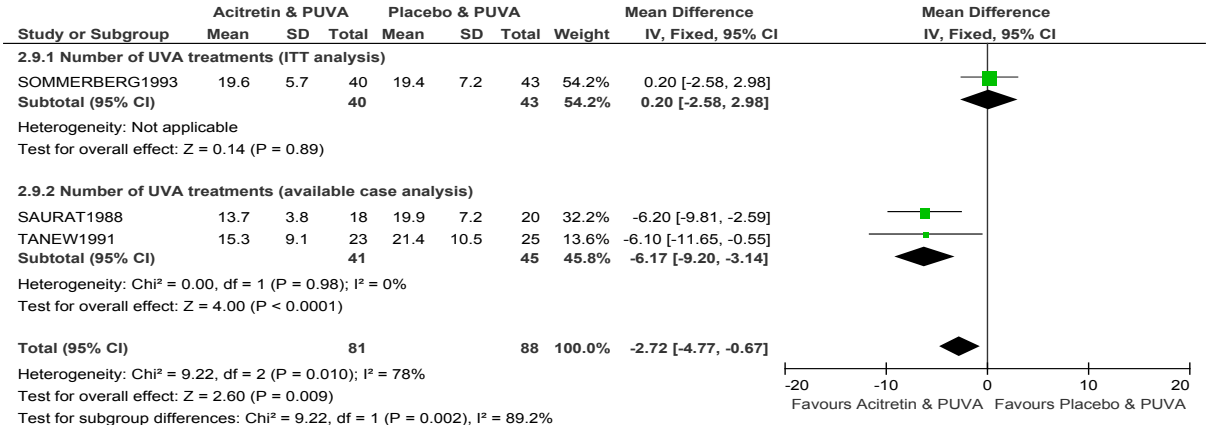


Figure 172: Withdrawal due to drug toxicity at 8-12 weeks

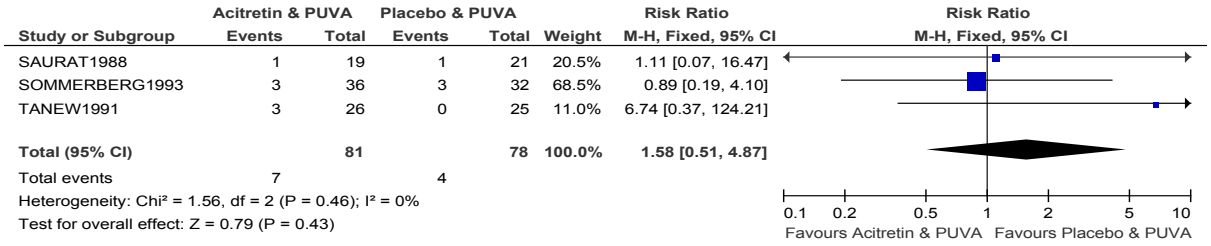
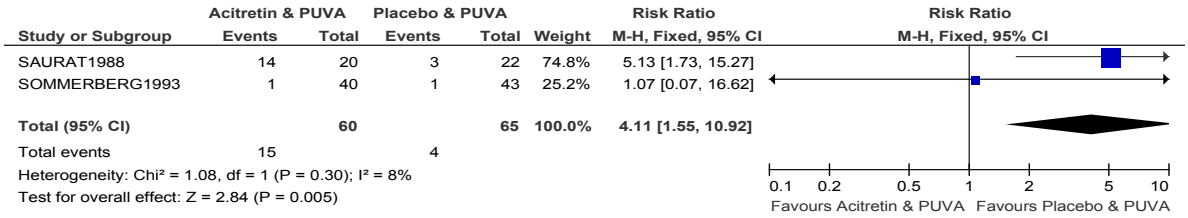


Figure 173: Severe adverse events at 12 weeks



J.6 Dithranol, coal tar and vitamin D or vitamin D analogues combined with UVB

J.6.1 Vitamin D or vitamin D analogue plus NBUVB vs vitamin D or vitamin D analogue alone

Figure 174: Clearance at 3 months

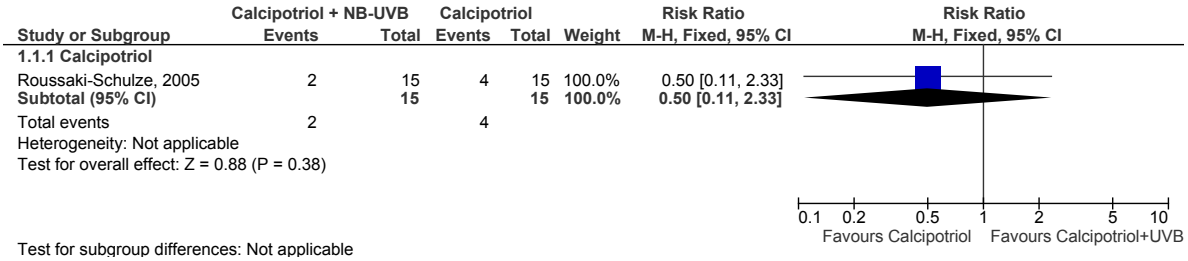


Figure 175: PASI50 at 3 months

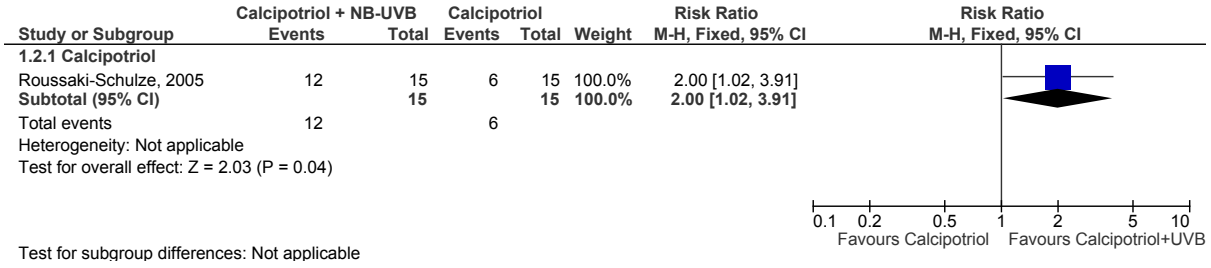


Figure 176: Mean reduction in PASI at 3 months

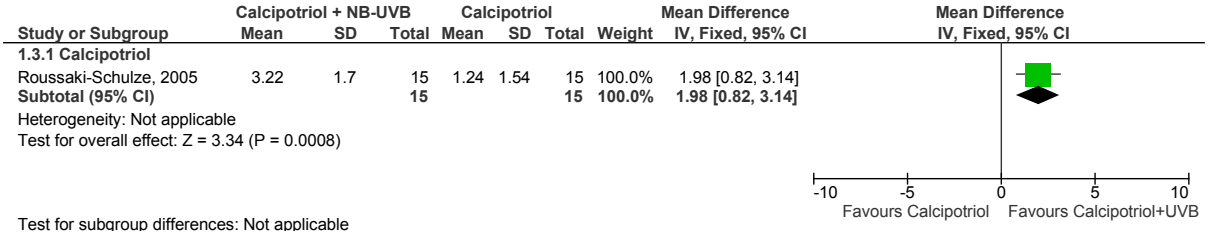
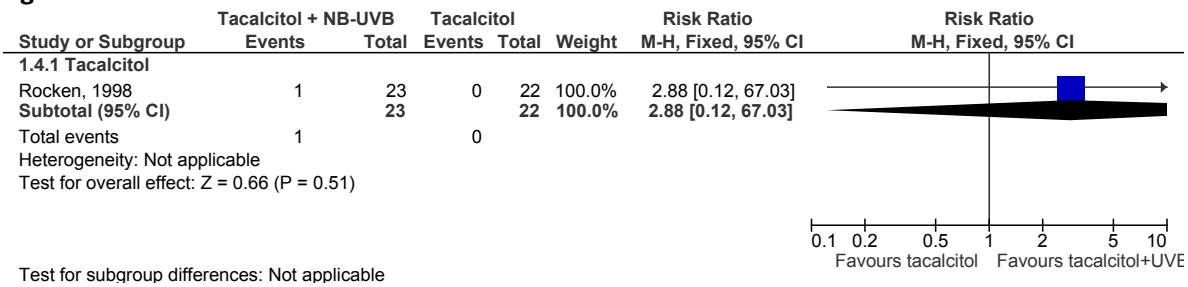


Figure 177: Withdrawal due to adverse events at 3 weeks

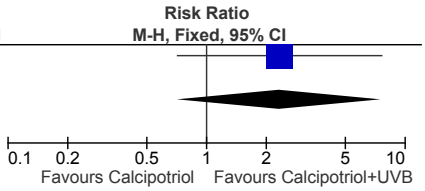


J.6.2 Calcipotriol plus BBUVB versus Calcipotriol

Figure 178: Clearance at 8 weeks

Study or Subgroup	Calcipotriol + BB-UVB Events	Total	Calcipotriol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kragballe, 1990	7	18	3	18	100.0%	2.33 [0.71, 7.63]
Total (95% CI)		**18**		**18**	**100.0%**	**2.33 [0.71, 7.63]**
Total events	7		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)



J.6.3 Calcipotriol plus NBUVB vs Placebo plus NBUVB

Figure 179: Clearance at 6 weeks

Study or Subgroup	Calcipotriol + NB-UVB Events	Total	Placebo + NB-UVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rim, 2002	9	10	11	18	100.0%	1.47 [0.97, 2.25]
Total (95% CI)		**10**		**18**	**100.0%**	**1.47 [0.97, 2.25]**
Total events	9		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)

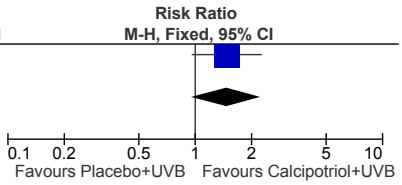


Figure 180: Percentage change in PASI

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Brands, 1999	3.8	12.99701	100.0%	3.80 [-21.67, 29.27]
Total (95% CI)			**100.0%**	**3.80 [-21.67, 29.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)

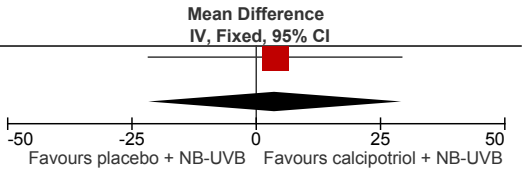


Figure 181: Change in PASI at 6.7 weeks

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Woo, 2003	2	1.94	100.0%	2.00 [-1.80, 5.80]
Total (95% CI)			**100.0%**	**2.00 [-1.80, 5.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

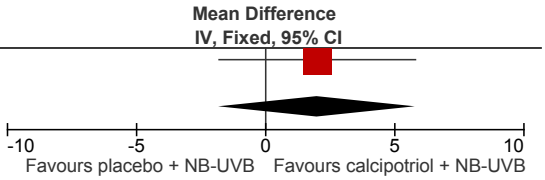


Figure 182: Mean number of UVB treatments (trunk) at 6 weeks

Study or Subgroup	Calcipotriol + NB-UVB Mean	SD	Total	Placebo + NB-UVB Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rim, 2002	14.3	5.8	10	15.7	4.1	18	100.0%	-1.40 [-5.46, 2.66]
Total (95% CI)			**10**			**18**	**100.0%**	**-1.40 [-5.46, 2.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

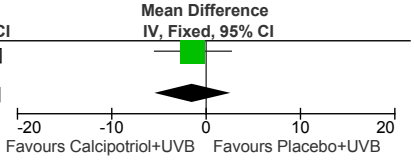


Figure 183: Mean number of UVB treatments (extremities) at 6 weeks

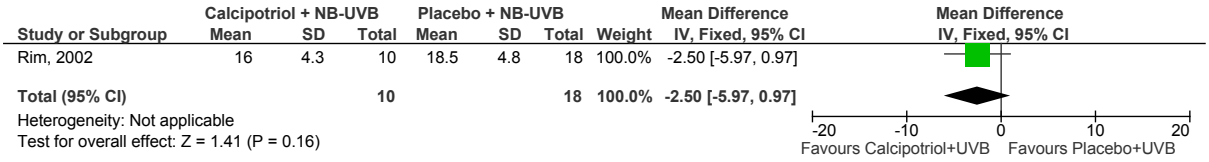


Figure 184: Mean number of UVB treatments at 6 weeks

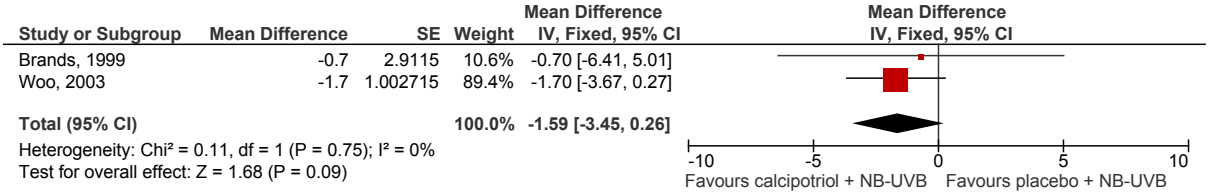


Figure 185: Mild to moderate burn at 6 weeks

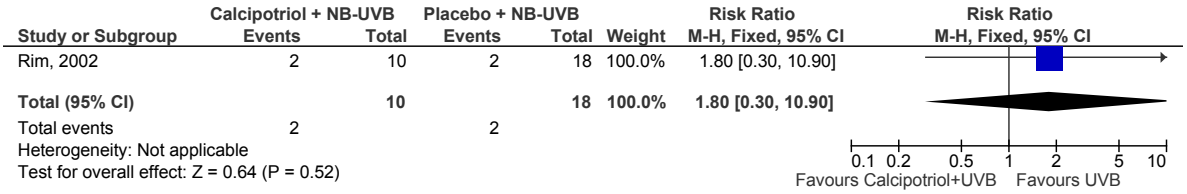
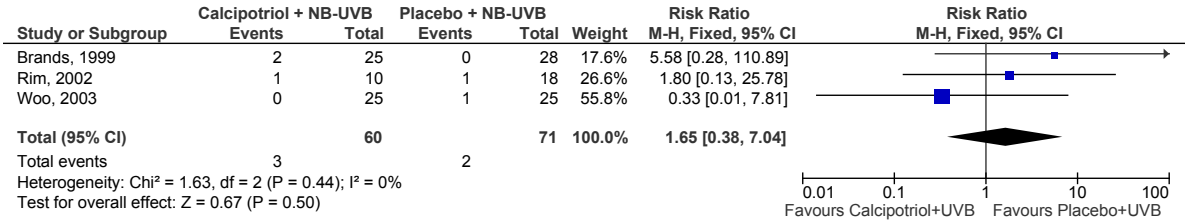
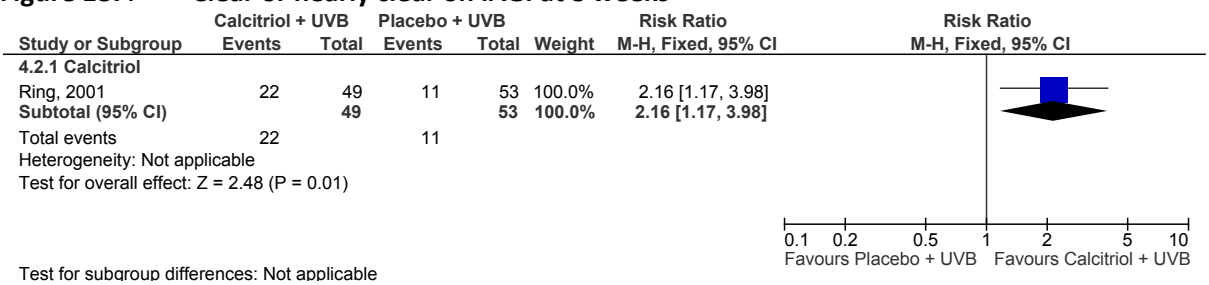


Figure 186: Withdrawal due to adverse events at 6-6.7 weeks



J.6.4 Vitamin D or vitamin D analogues plus BBUVB vs Placebo plus BBUVB

Figure 187: Clear or nearly clear on IAGI at 8 weeks



Test for subgroup differences: Not applicable

Figure 188: Clearance at 3 months

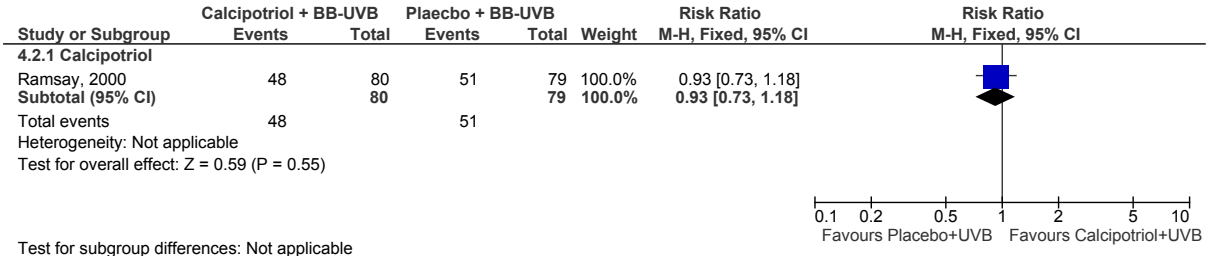


Figure 189: Number of UV treatments for clearance at 3 months

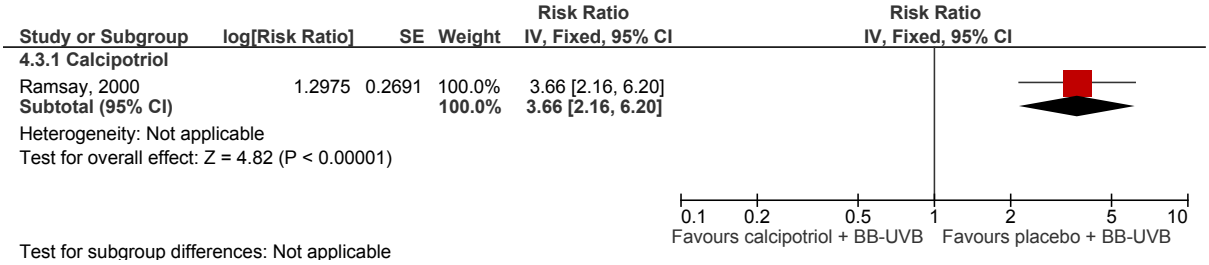


Figure 190: Modified PASI80 at 3 months

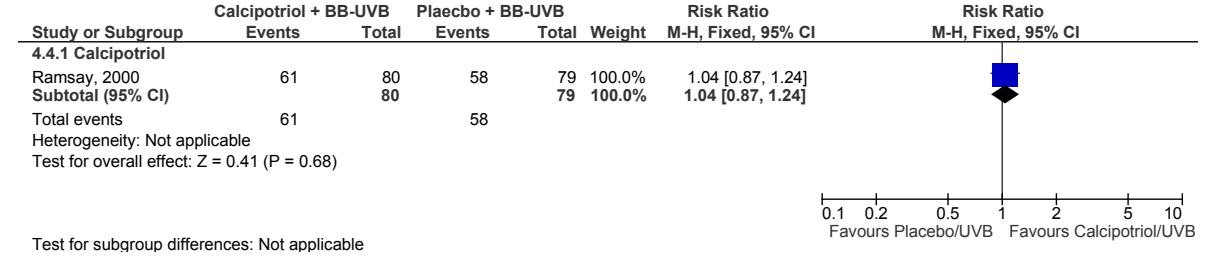


Figure 191: Number of UV treatments for modified PASI80 at 3 months

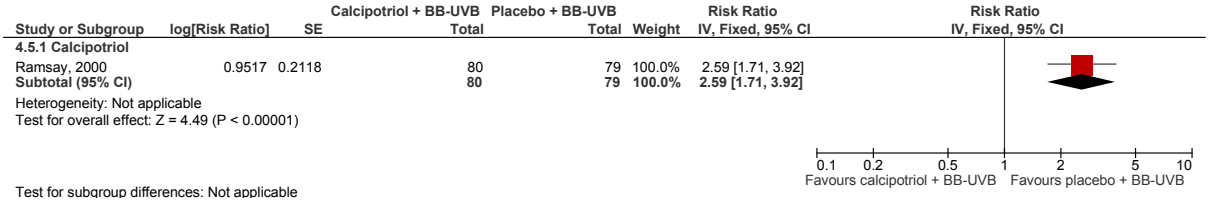


Figure 192: Percentage change in modified PASI at 3 months

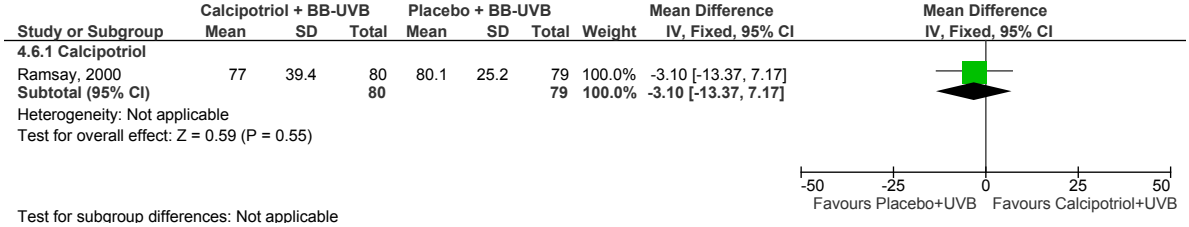


Figure 193: Relapse rate post-treatment among clearers at 12 weeks post treatment

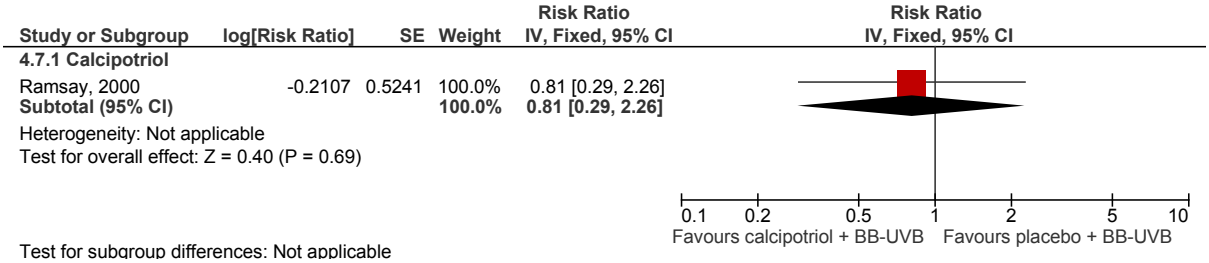


Figure 194: Burn/erythema/pruritis

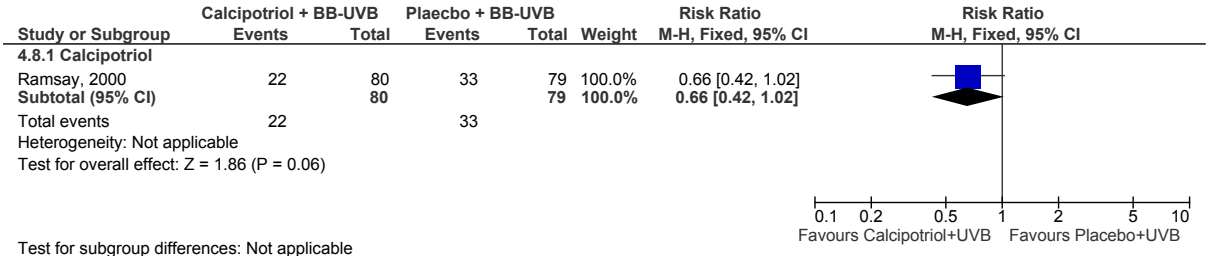
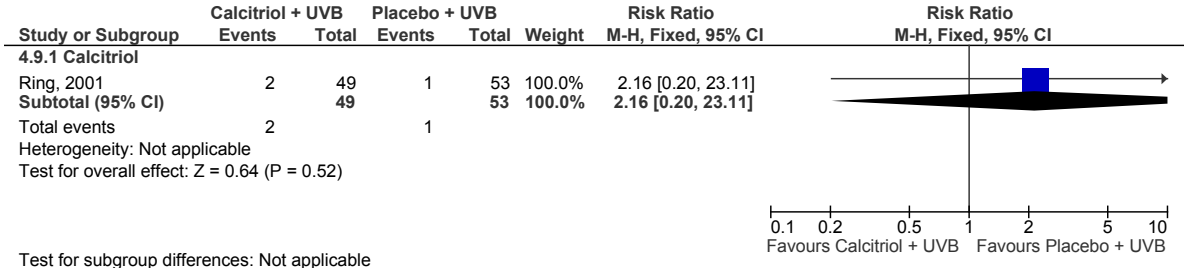


Figure 195: Withdrawal due to adverse events at 8 weeks



J.6.5 LCD plus NBUVB vs NBUVB

Figure 196: Clearance at 12 weeks

Study or Subgroup	LCD + NB-UVB Events	Total	NB-UVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bagel, 2009	7	12	6	12	100.0%	1.17 [0.56, 2.45]
Total (95% CI)		**12**		**12**	**100.0%**	**1.17 [0.56, 2.45]**
Total events	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

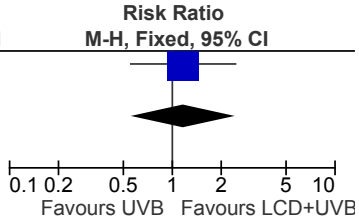
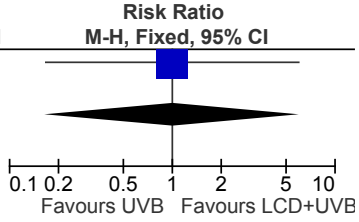


Figure 197: Moderate burn at 12 weeks

Study or Subgroup	LCD + NB-UVB Events	Total	NB-UVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bagel, 2009	2	12	2	12	100.0%	1.00 [0.17, 5.98]
Total (95% CI)		**12**		**12**	**100.0%**	**1.00 [0.17, 5.98]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

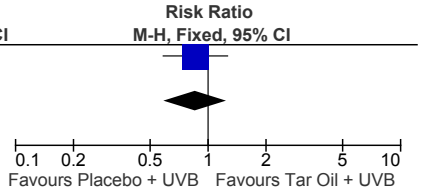


J.6.6 Tar oil plus sub-erythemogenic BBUVB vs Placebo plus maximally erythemogenic BBUVB

Figure 198: Clearance at 12 weeks

Study or Subgroup	Tar Oil+lowUVB Events	Total	Placebo+highUVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menkes, 1985	19	30	14	19	100.0%	0.86 [0.59, 1.26]
Total (95% CI)		**30**		**19**	**100.0%**	**0.86 [0.59, 1.26]**
Total events	19		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)



J.6.7 Dithranol plus BBUVB vs Dithranol alone

Figure 199: Clear or nearly clear (≤1% BSA, ≤1 on all severity scores) at 8 weeks

Study or Subgroup	Dithranol + BB-UVB Events	Total	Dithranol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerritsen, 1998	15	24	7	24	100.0%	2.14 [1.07, 4.30]
Total (95% CI)		**24**		**24**	**100.0%**	**2.14 [1.07, 4.30]**
Total events	15		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)

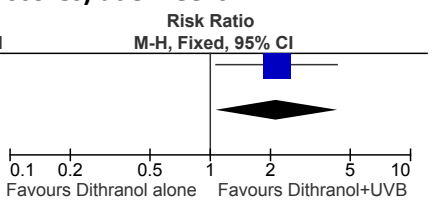
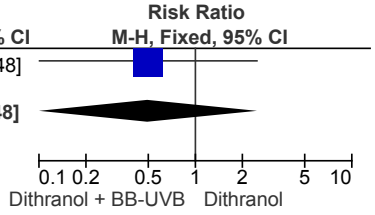


Figure 200: Irritation (requiring adjustment of dithranol) at 8 weeks

Study or Subgroup	Dithranol + BB-UVB Events	Total	Dithranol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerritsen, 1998	2	24	4	24	100.0%	0.50 [0.10, 2.48]
Total (95% CI)		**24**		**24**	**100.0%**	**0.50 [0.10, 2.48]**
Total events	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.40)

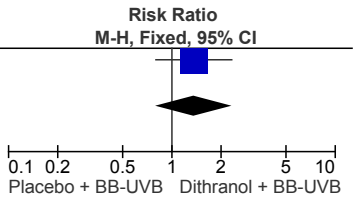


J.6.8 Dithranol plus BBUVB vs Placebo plus BBUVB

Figure 201: Clear or nearly clear (≤1% BSA, ≤1 on all severity scores) at 8 weeks

Study or Subgroup	Dithranol + BB-UVB Events	Total	Placebo + BB-UVB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gerritsen, 1998	15	24	11	24	100.0%	1.36 [0.80, 2.33]
Total (95% CI)		**24**		**24**	**100.0%**	**1.36 [0.80, 2.33]**
Total events	15		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)



J.6.9 Dithranol plus coal tar plus BBUVB vs dithranol

Figure 202: Clearance at 3 weeks

Study or Subgroup	Dithranol + Coal Tar + UV Events	Total	Dithranol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Paramsothy, 1988	20	27	16	26	100.0%	1.20 [0.83, 1.75]
Total (95% CI)		**27**		**26**	**100.0%**	**1.20 [0.83, 1.75]**
Total events	20		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

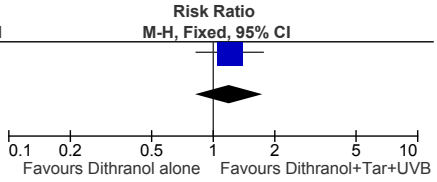


Figure 203: Mean number of days to clearance at 3 weeks

Study or Subgroup	Dithranol + Coal Tar + UV Mean	SD	Total	Dithranol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Paramsothy, 1988	20.3	1.6	27	19.5	2.6	26	100.0%	0.80 [-0.37, 1.97]
Total (95% CI)			**27**			**26**	**100.0%**	**0.80 [-0.37, 1.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

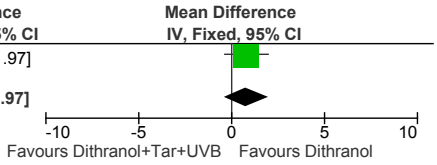
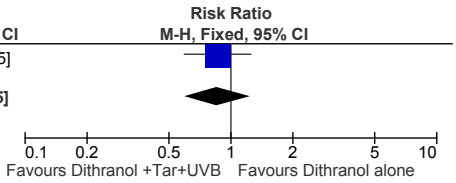


Figure 204: Relapse rate post-treatment

Study or Subgroup	Dithranol + Coal Tar + UV Events	Total	Dithranol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Paramsothy, 1988	14	20	13	16	100.0%	0.86 [0.59, 1.25]
Total (95% CI)		**20**		**16**	**100.0%**	**0.86 [0.59, 1.25]**
Total events	14		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



J.7 Systemic therapy

J.7.1 Methotrexate vs placebo for maintenance of remission

Figure 205: PASI90 at 16 weeks

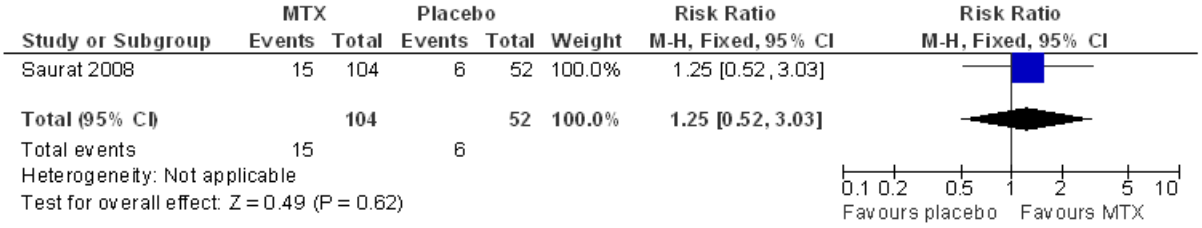


Figure 206: Clear/nearly clear on PGA at 16 weeks

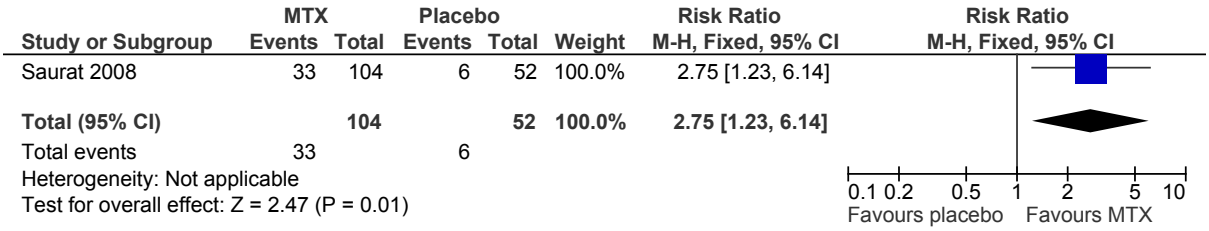


Figure 207: PASI75 at 4-6 months

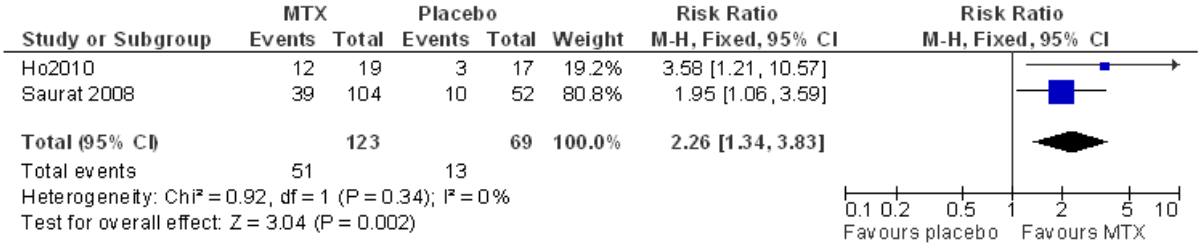


Figure 208: PASI50 at 4-6 months

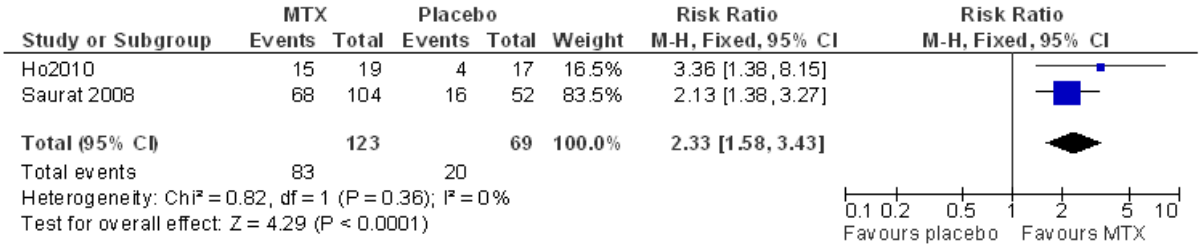


Figure 209: PASI change/final score at 4-6 months

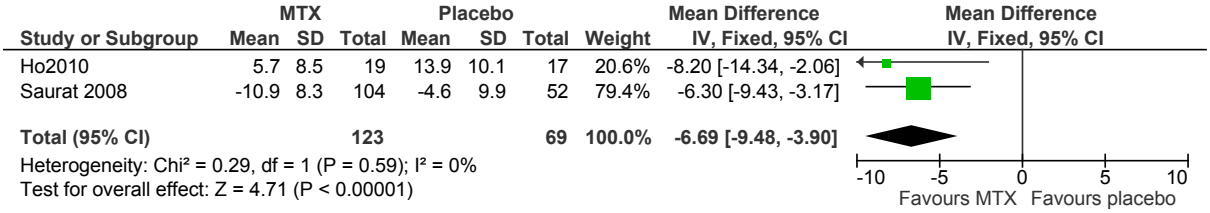


Figure 210: Severe adverse events at 26 weeks

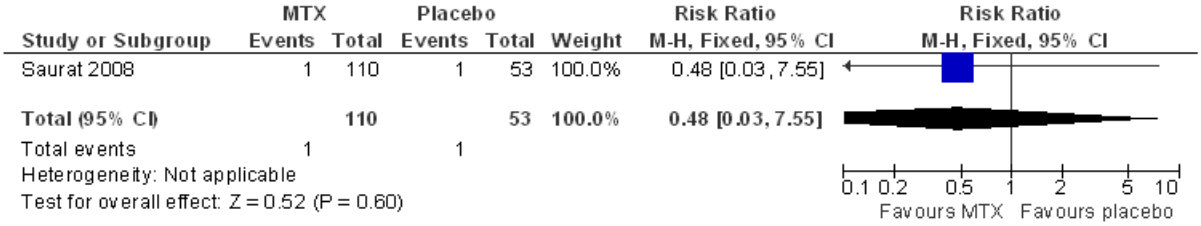


Figure 211: Withdrawal due to toxicity at 26 weeks

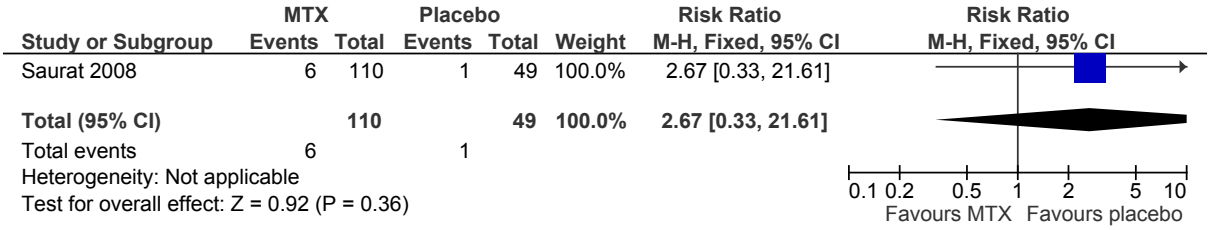
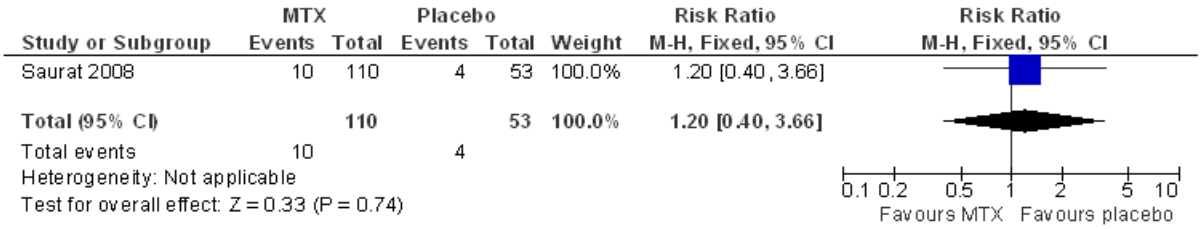


Figure 212: Raised liver enzymes at 26 weeks



J.7.2 Methotrexate vs ciclosporin for induction of remission

Figure 213: Clear/nearly clear (PASI90) at 12-16 weeks

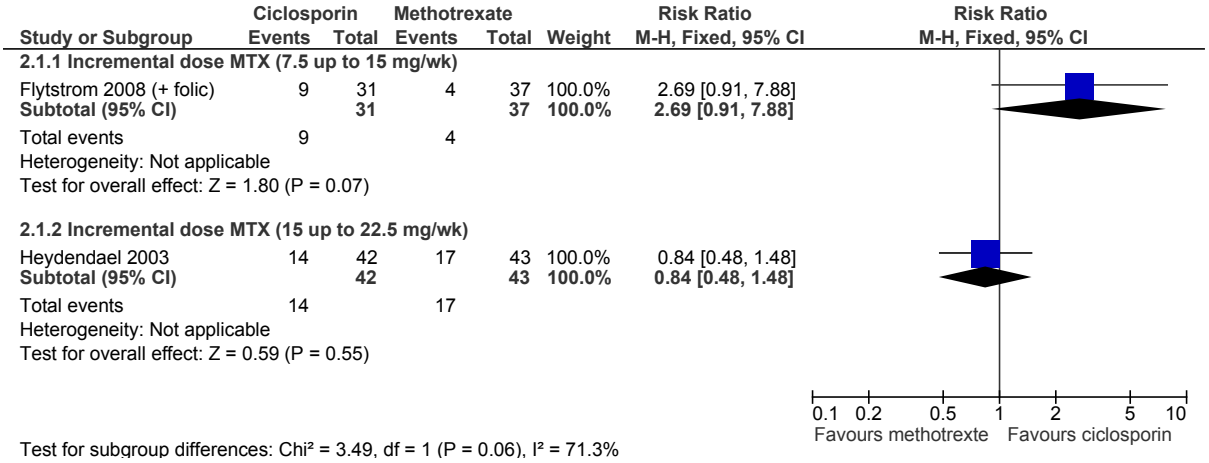


Figure 214: Clearanceat 10 weeks

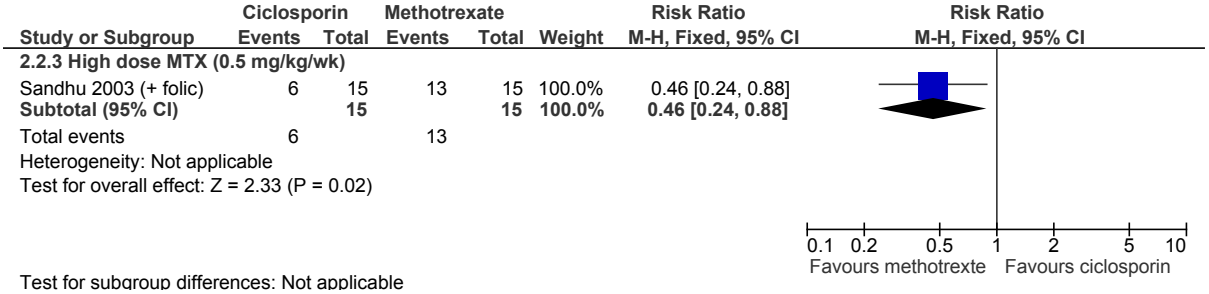


Figure 215: Time to remission (follow-up for a maximum of 16 weeks)

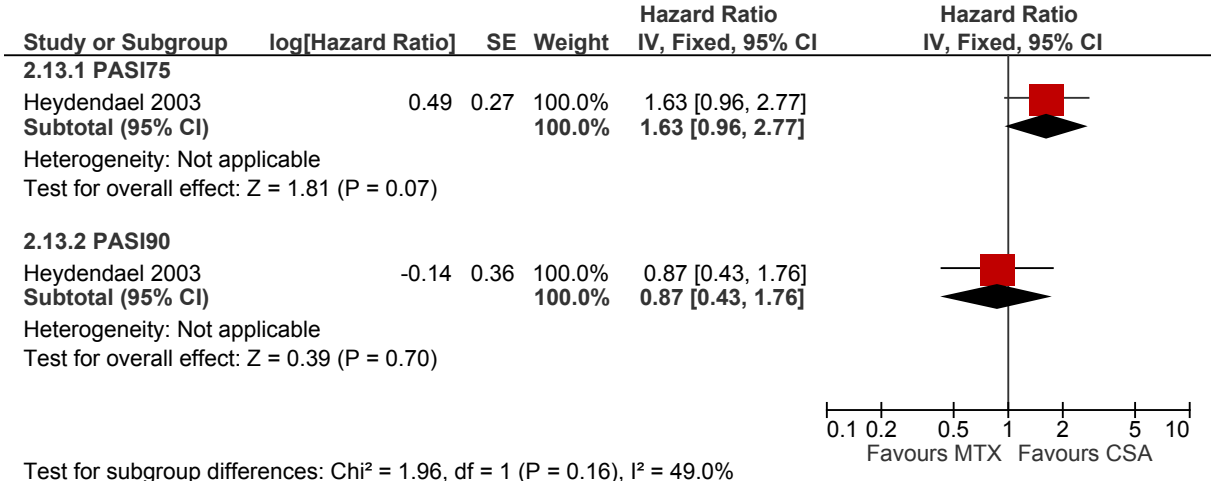


Figure 216: PASI75 at 12-16 weeks

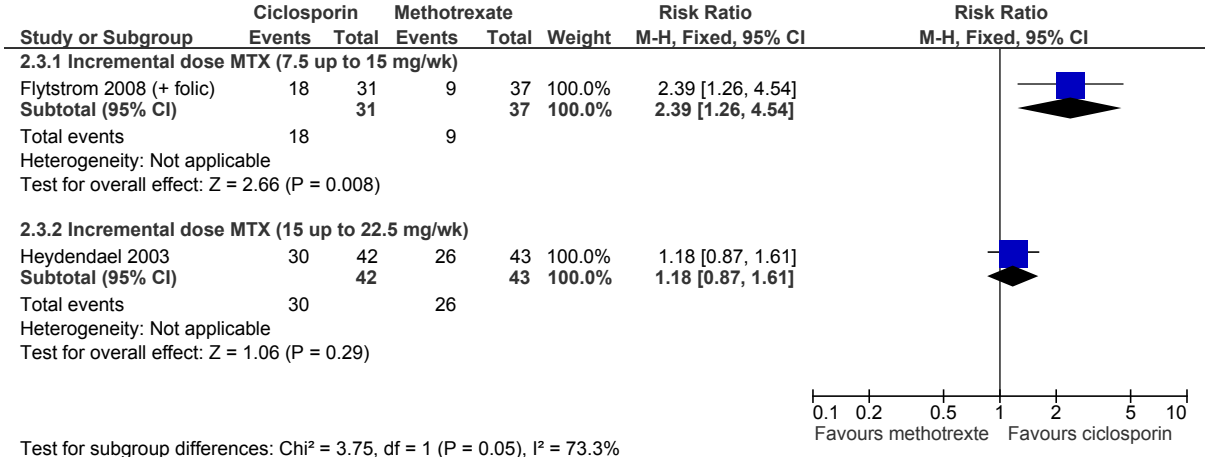


Figure 217: PASI50 at 12 weeks

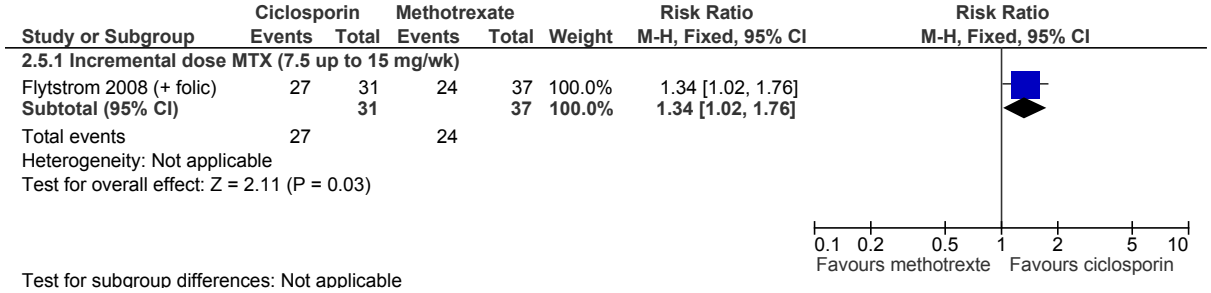


Figure 218: Final PASI at 12-16 weeks

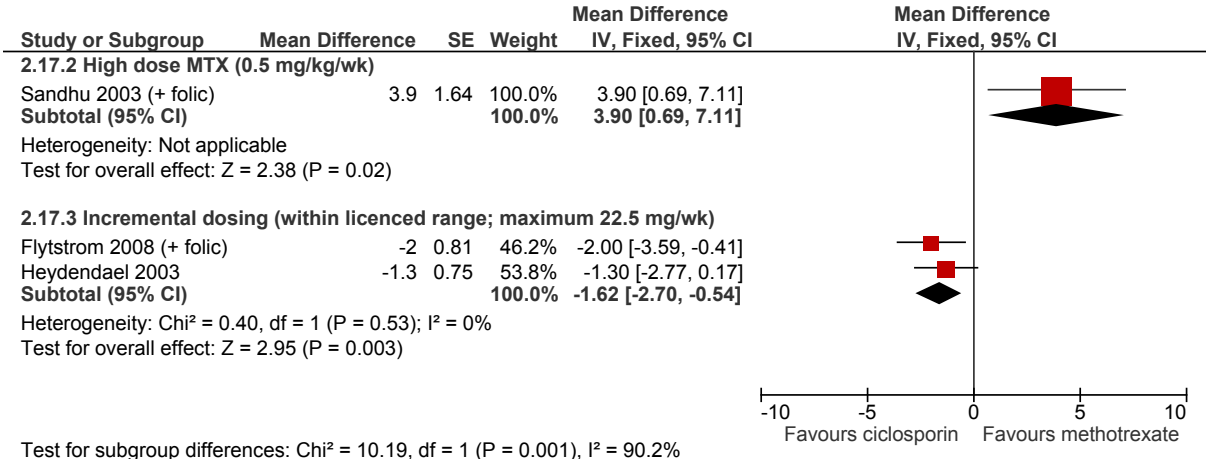


Figure 219: Change in NAPSI at 6 months

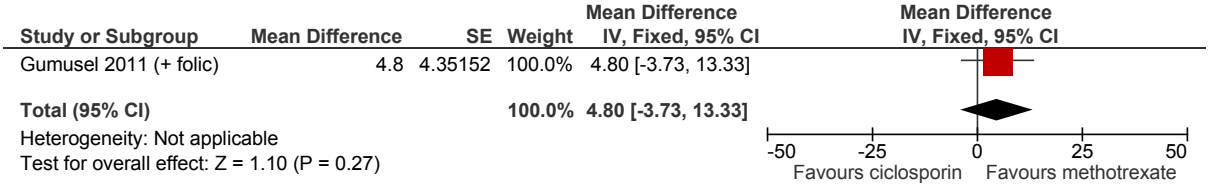


Figure 220: Remaining clear at 12 weeks (after tapering)

Study or Subgroup	Ciclosporin Events	Ciclosporin Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sandhu 2003 (+ folic)	2	6	13	13	100.0%	0.37 [0.14, 1.01]
Total (95% CI)		**6**		**13**	**100.0%**	**0.37 [0.14, 1.01]**
Total events	2		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)

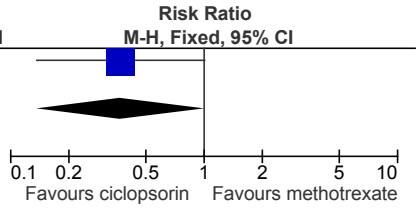


Figure 221: Elevated liver enzymes at 12-24 weeks

Study or Subgroup	Ciclosporin Events	Ciclosporin Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Flytstrom 2008 (+ folic)	0	31	7	37	33.0%	0.08 [0.00, 1.33]
Gumusel 2011 (+ folic)	0	19	1	18	7.4%	0.32 [0.01, 7.30]
Heydendael 2003	0	42	12	43	59.5%	0.04 [0.00, 0.67]
Total (95% CI)		**92**		**98**	**100.0%**	**0.07 [0.01, 0.38]**
Total events	0		20			

Heterogeneity: Chi² = 1.00, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)

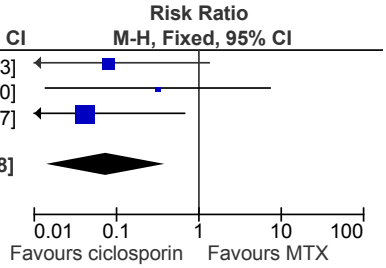


Figure 222: Elevated creatinine at 12-24 weeks

Study or Subgroup	Ciclosporin Events	Ciclosporin Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Flytstrom 2008 (+ folic)	6	31	0	37	47.1%	15.44 [0.90, 263.63]
Gumusel 2011 (+ folic)	2	19	0	18	52.9%	4.75 [0.24, 92.65]
Total (95% CI)		**50**		**55**	**100.0%**	**9.79 [1.32, 72.65]**
Total events	8		0			

Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

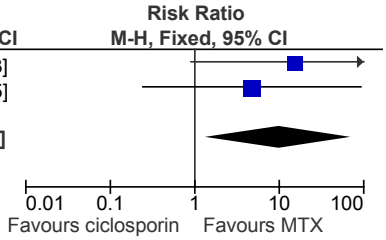


Figure 223: Hypertension at 12-16 weeks

Study or Subgroup	Ciclosporin Events	Ciclosporin Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 Incremental dose MTX (15 up to 22.5 mg/wk)						
Heydendael 2003	2	42	0	43	100.0%	5.12 [0.25, 103.50]
Subtotal (95% CI)		**42**		**43**	**100.0%**	**5.12 [0.25, 103.50]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)

2.10.2 Diastolic hypertension - High dose MTX (0.5 mg/kg/wk)						
Sandhu 2003 (+ folic)	4	15	0	15	100.0%	9.00 [0.53, 153.79]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**9.00 [0.53, 153.79]**
Total events	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%

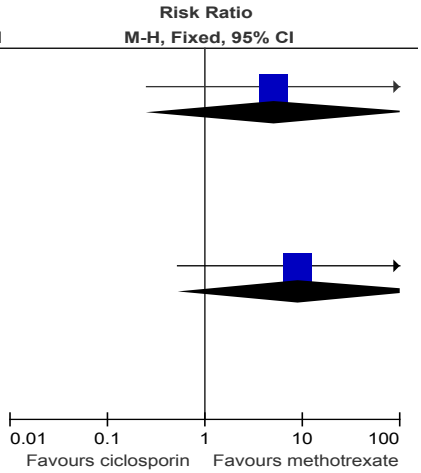
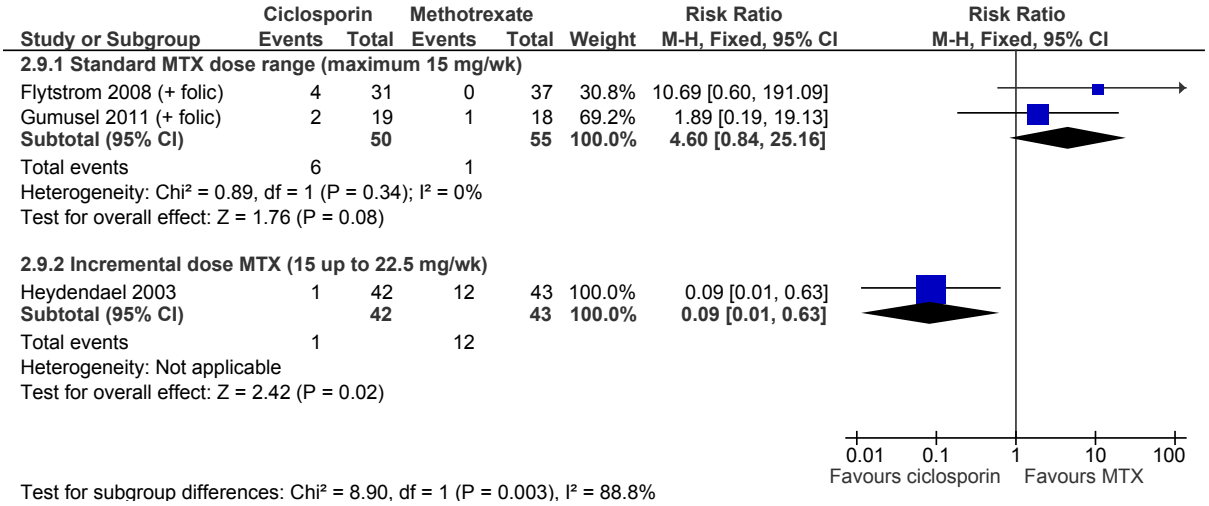


Figure 224: Withdrawal due to toxicity at 12-16 weeks



J.7.3 Acitretin vs placebo for induction of remission

Figure 225: PASI75 at 8 weeks

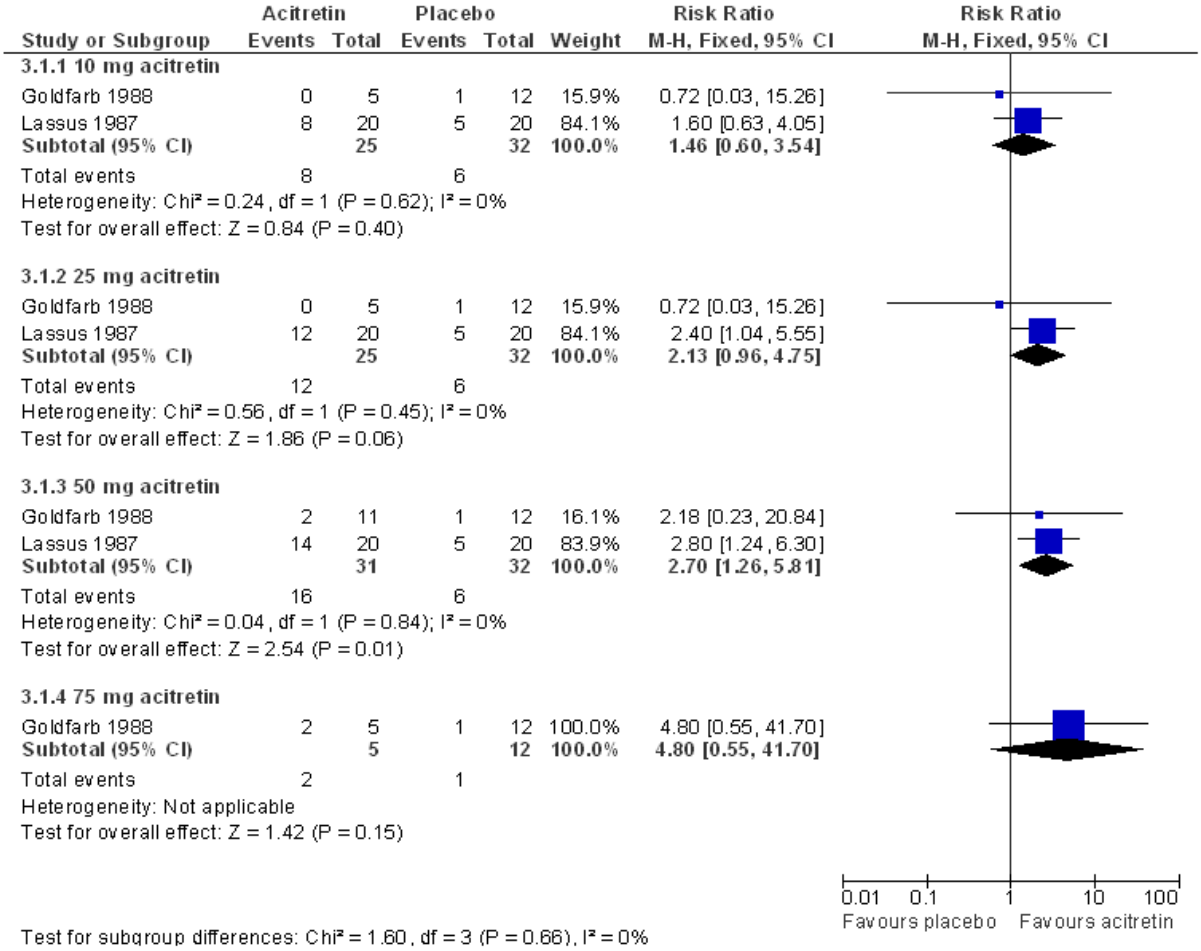


Figure 226: Cheilitis at 8 weeks

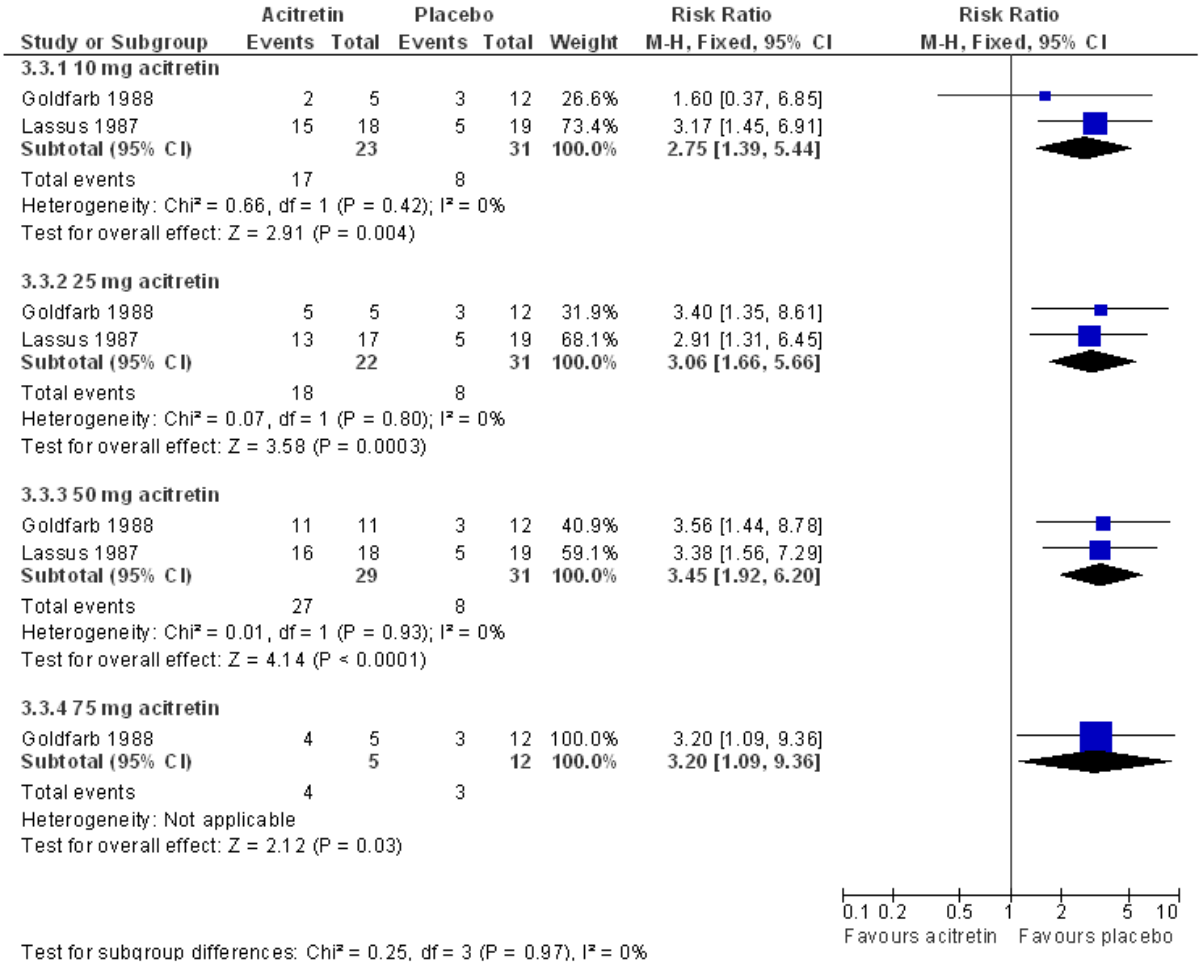


Figure 227: Cheilitis at 6 months

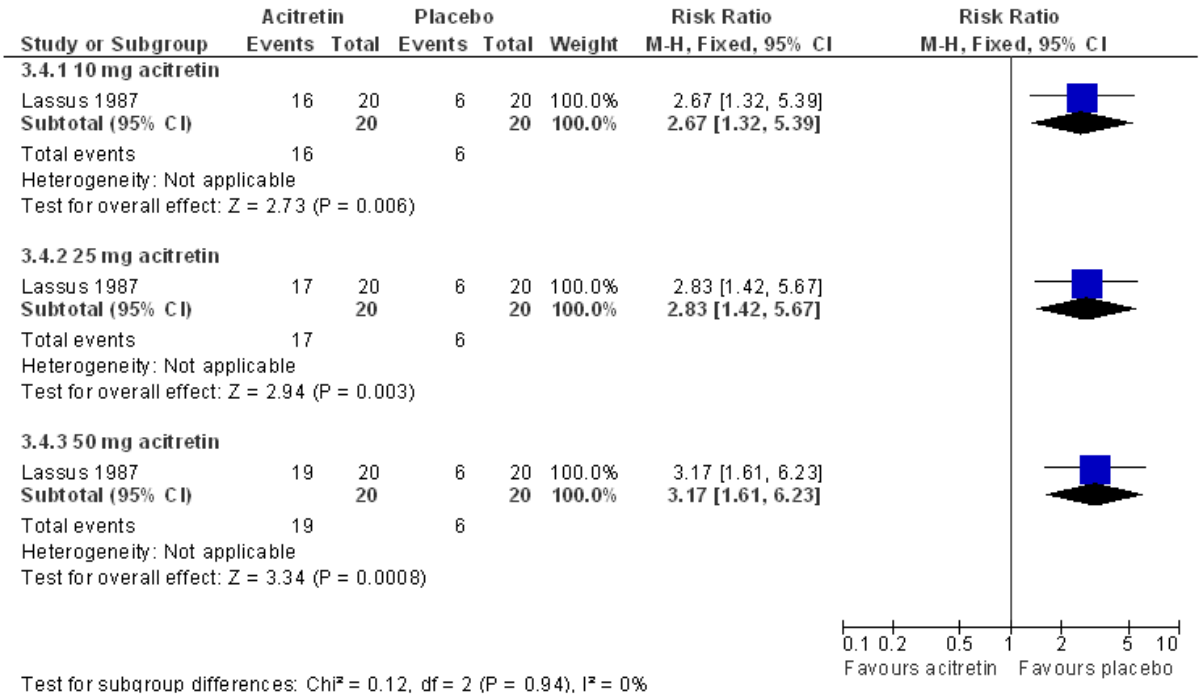


Figure 228: Hair loss at 6 months

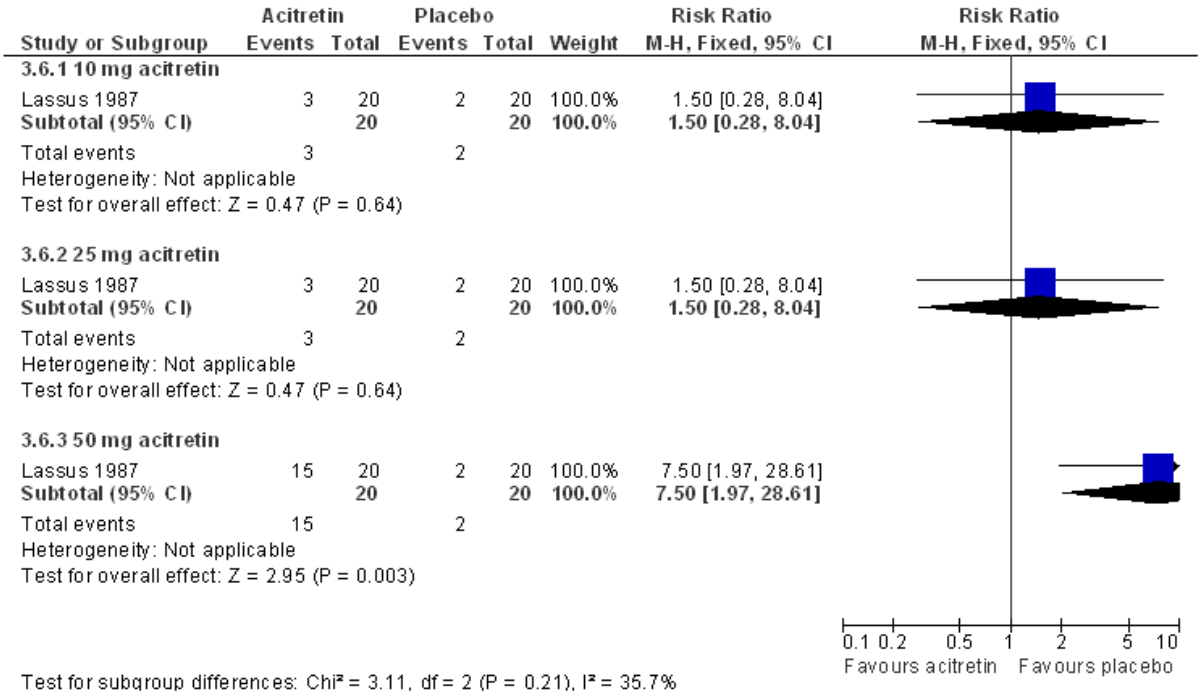


Figure 229: Increased triglycerides at 8 weeks

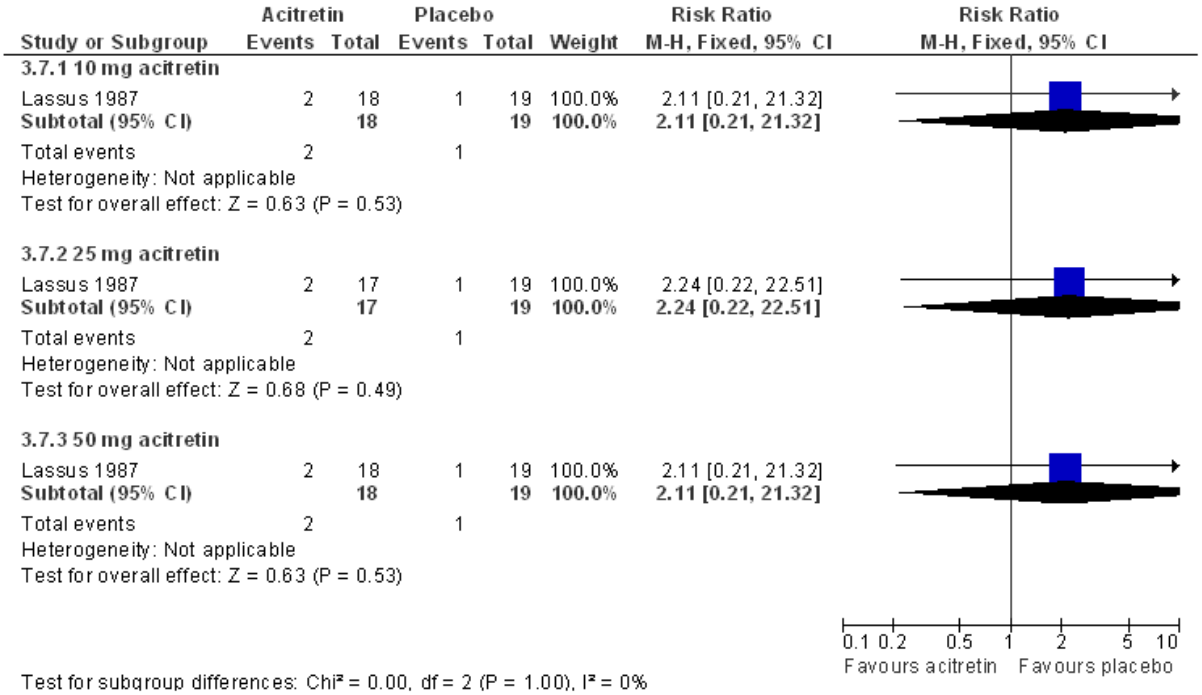


Figure 230: Increased triglycerides at 6 months

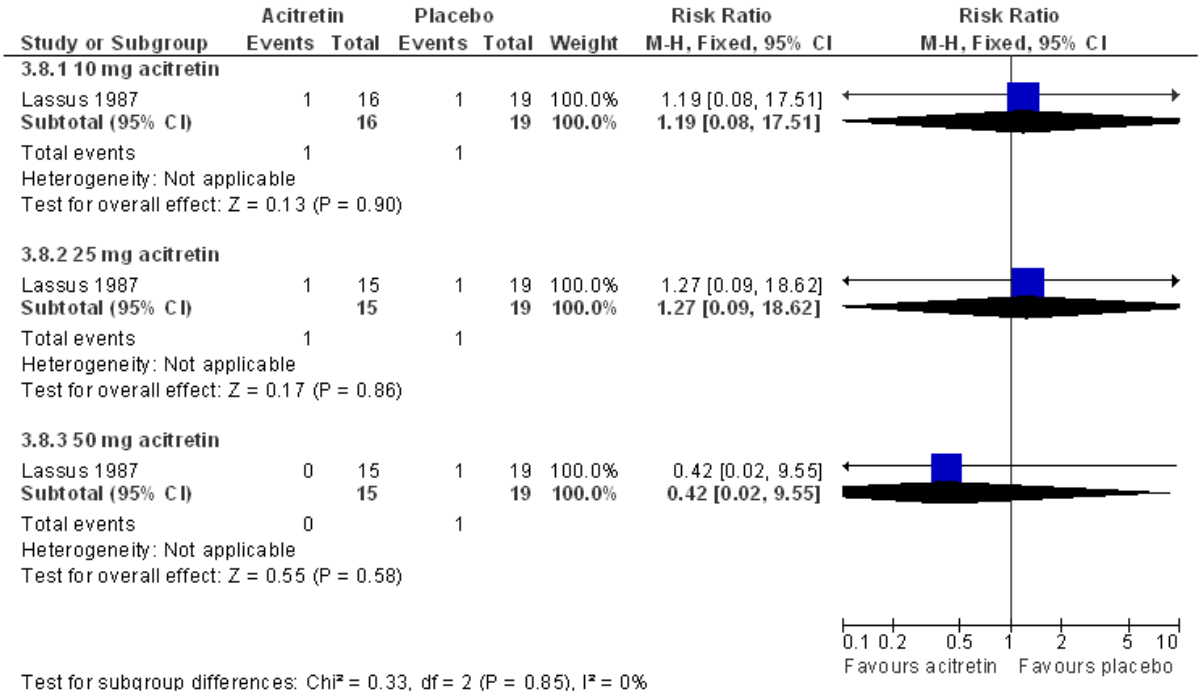


Figure 231: Increased liver enzymes at 8 weeks

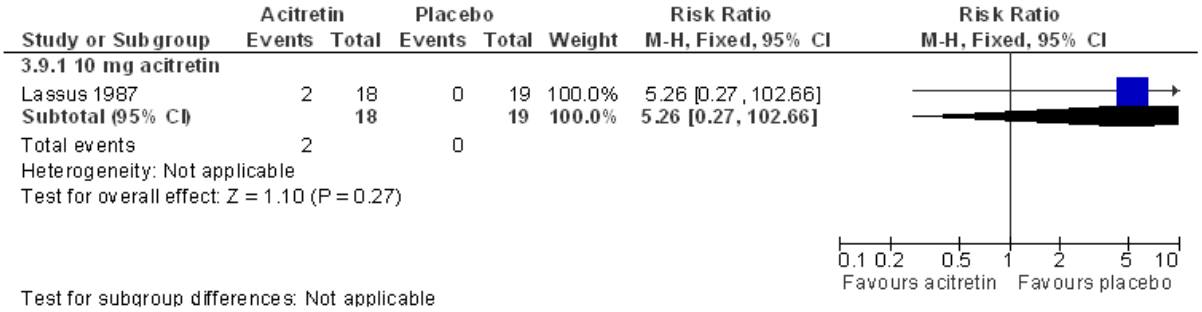


Figure 232: Increased liver enzymes at 6 months

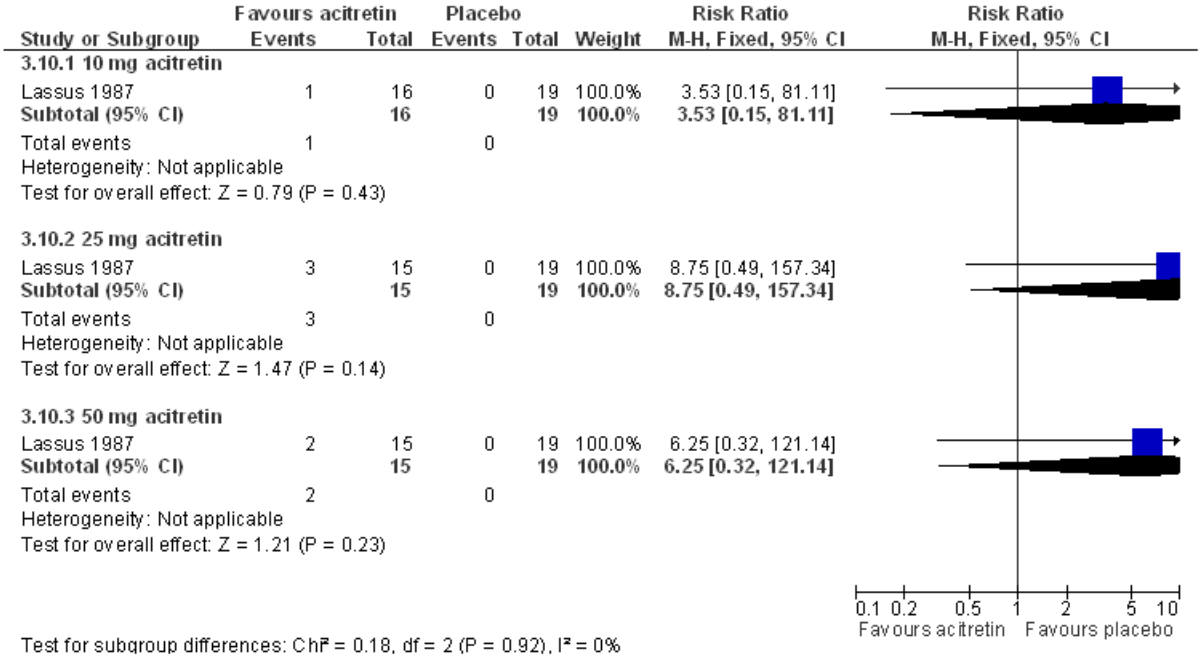


Figure 233: Increased cholesterol at 8 weeks

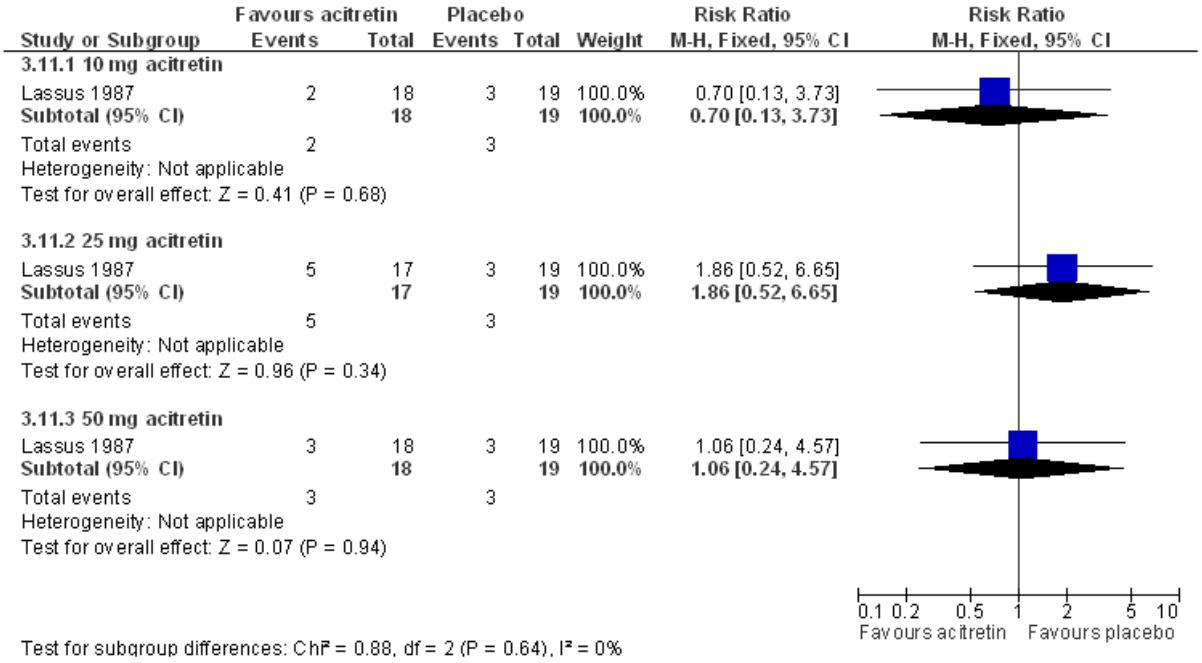


Figure 234: Increased cholesterol at 6 months

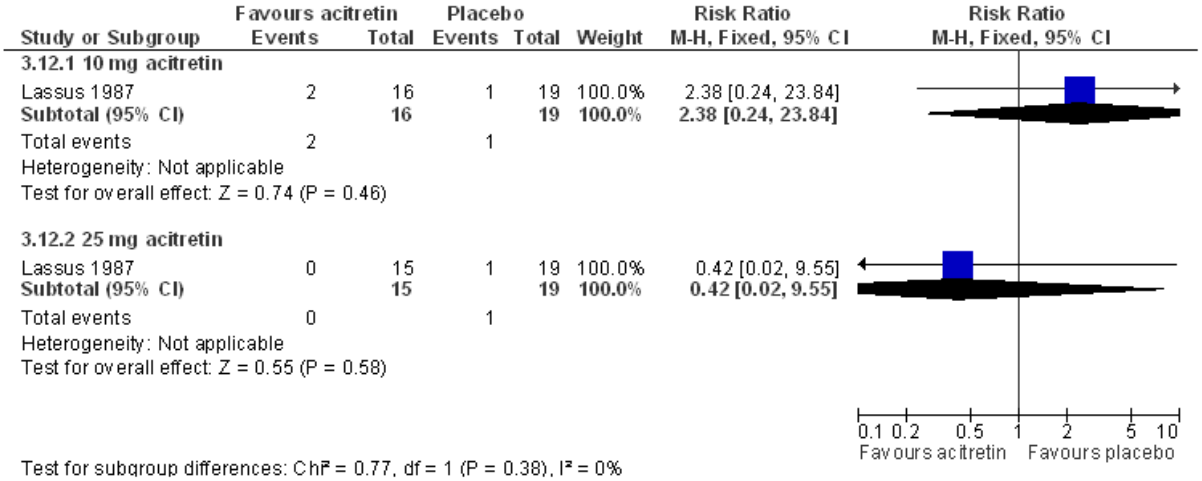
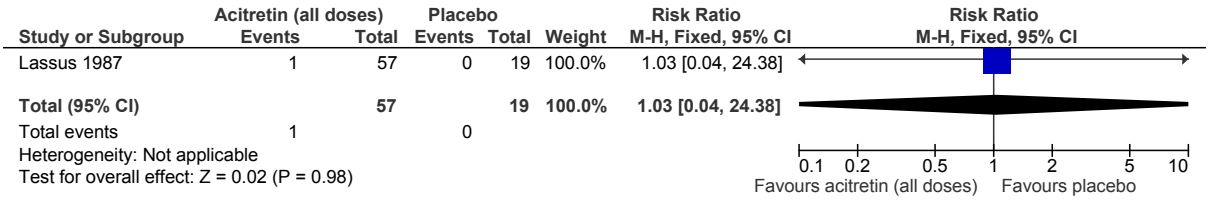


Figure 235: Withdrawal due to toxicity at 6 months



J.7.4 Increasing vs decreasing acitretin dosing schedule for induction of remission

Figure 236: Cheilitis at 6 weeks

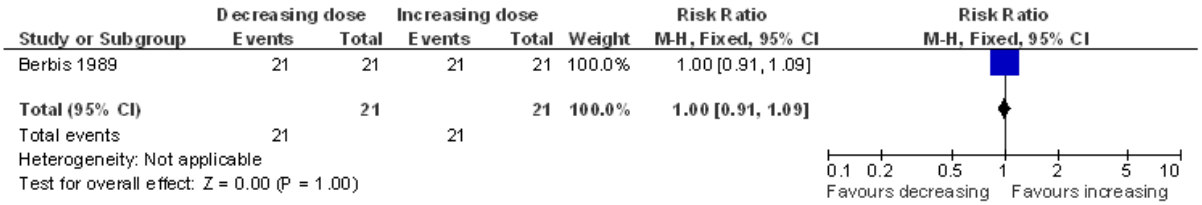


Figure 237: Hair loss at 6 weeks

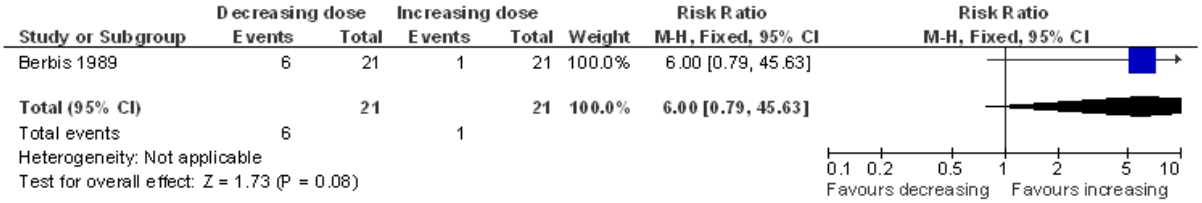
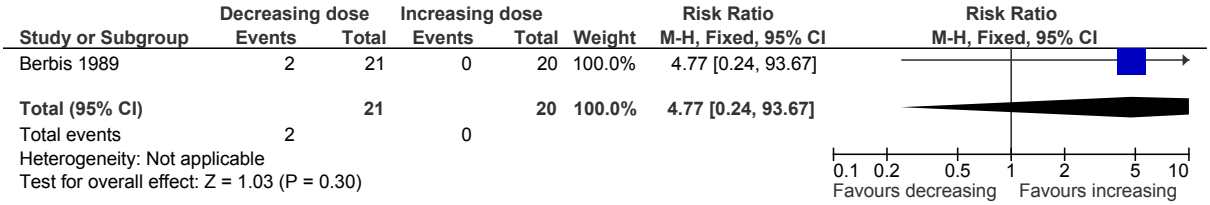


Figure 238: Withdrawal due to toxicity at 6 weeks



J.7.5 Increasing vs constant acitretin dosing schedule of induction of remission

Figure 239: Cheilitis at 6 weeks

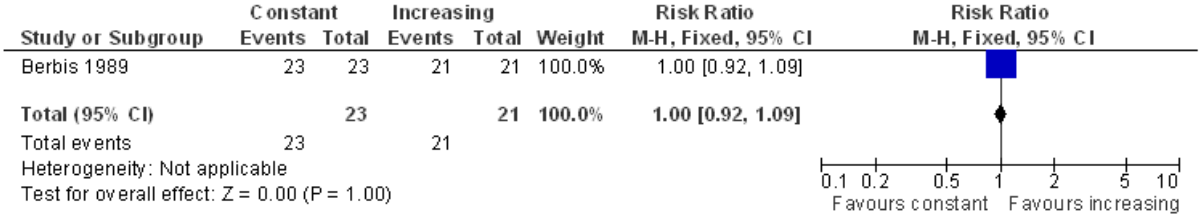


Figure 240: Hair loss at 6 weeks

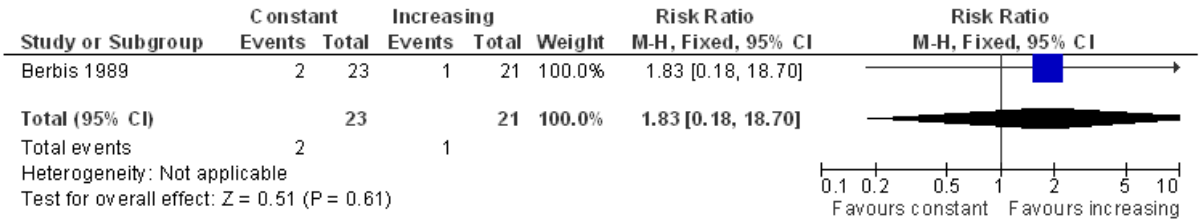
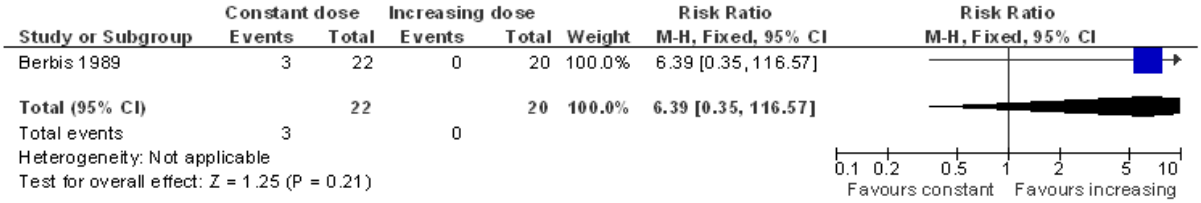
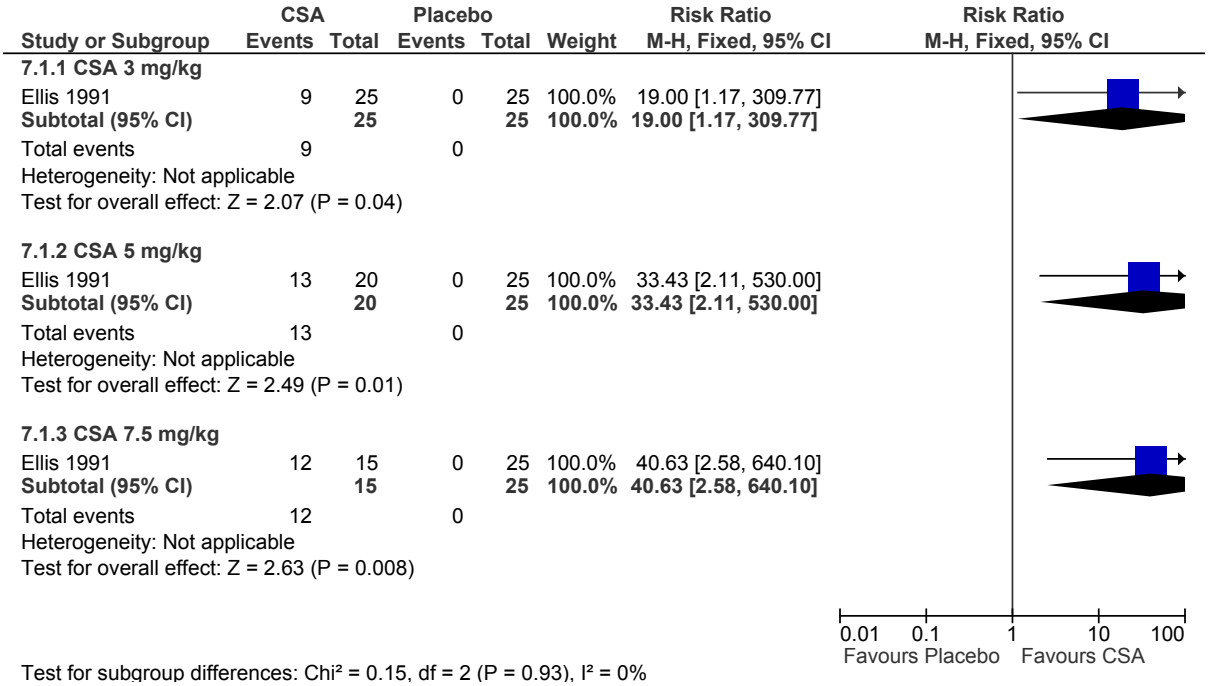


Figure 241: Withdrawal due to toxicity at 6 weeks



J.7.6 Ciclosporin vs placebo for induction of remission

Figure 242: Clear/nearly clear on PGA at 8 weeks



Test for subgroup differences: Chi² = 0.15, df = 2 (P = 0.93), I² = 0%

Figure 243: Clearance at 4 weeks

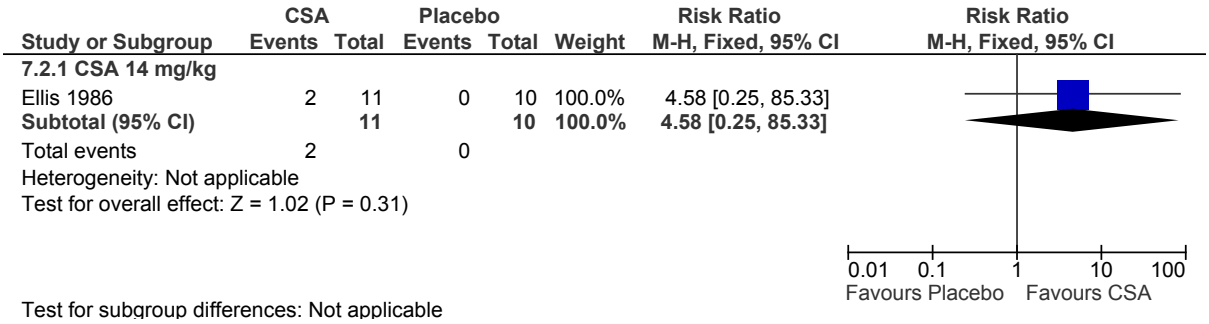


Figure 244: PASI75 at 8-10 weeks

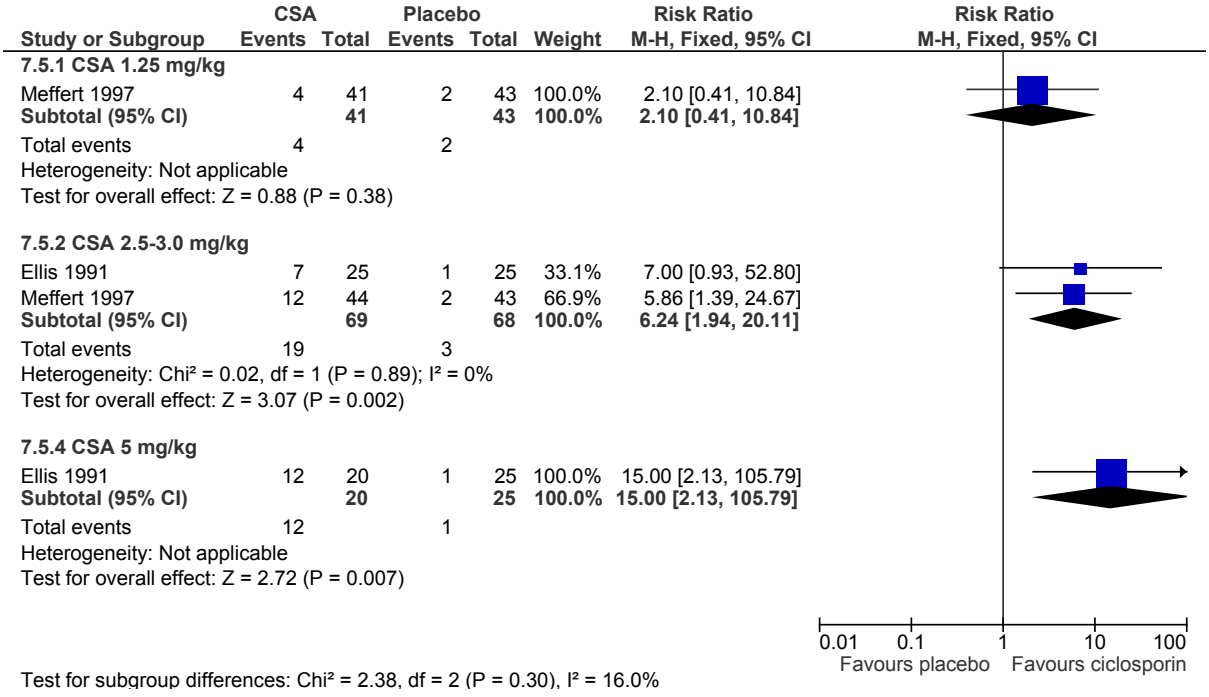


Figure 245: PASI50 at 4-10 weeks

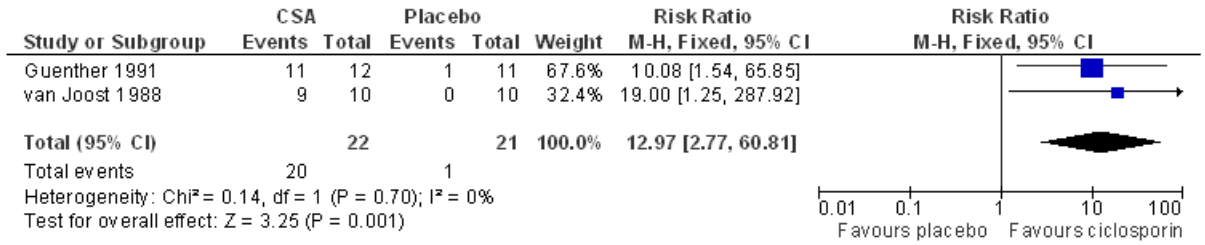
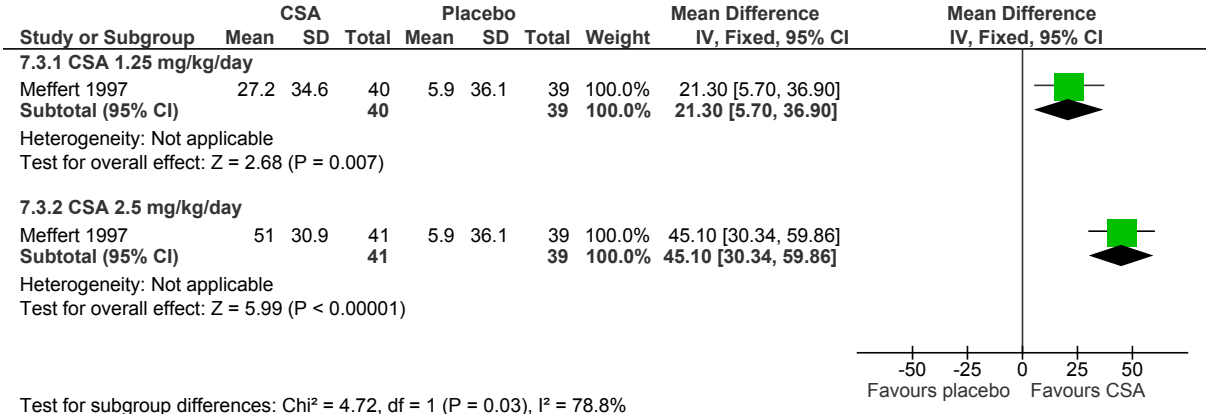


Figure 246: Percentage change in PASI at 10 weeks



Test for subgroup differences: Chi² = 4.72, df = 1 (P = 0.03), I² = 78.8%

Figure 247: Hypertension at 8-10 weeks

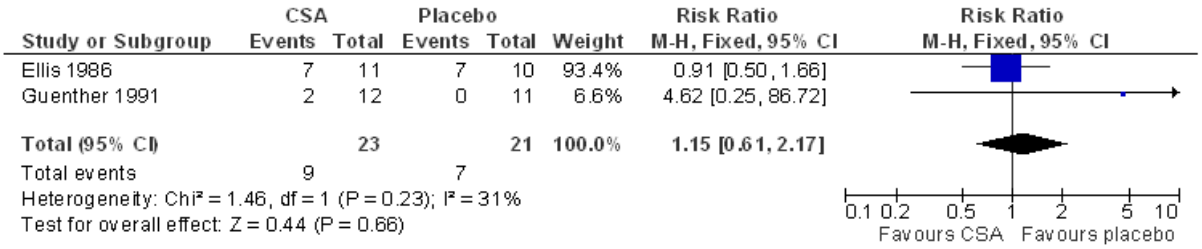
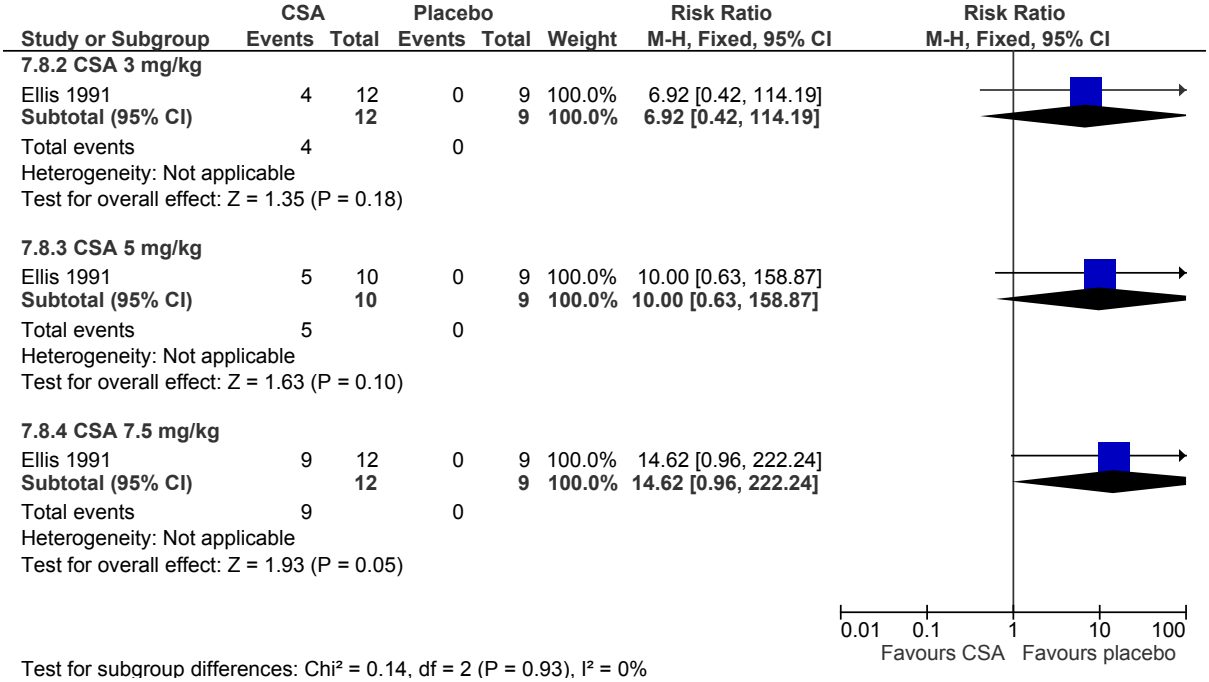


Figure 248: Decrease in glomerular filtration rate at 8 weeks



Test for subgroup differences: Chi² = 0.14, df = 2 (P = 0.93), I² = 0%

J.7.7 Ciclosporin dosage comparisons for induction of remission

Figure 249: PASI75 at 12-36 weeks

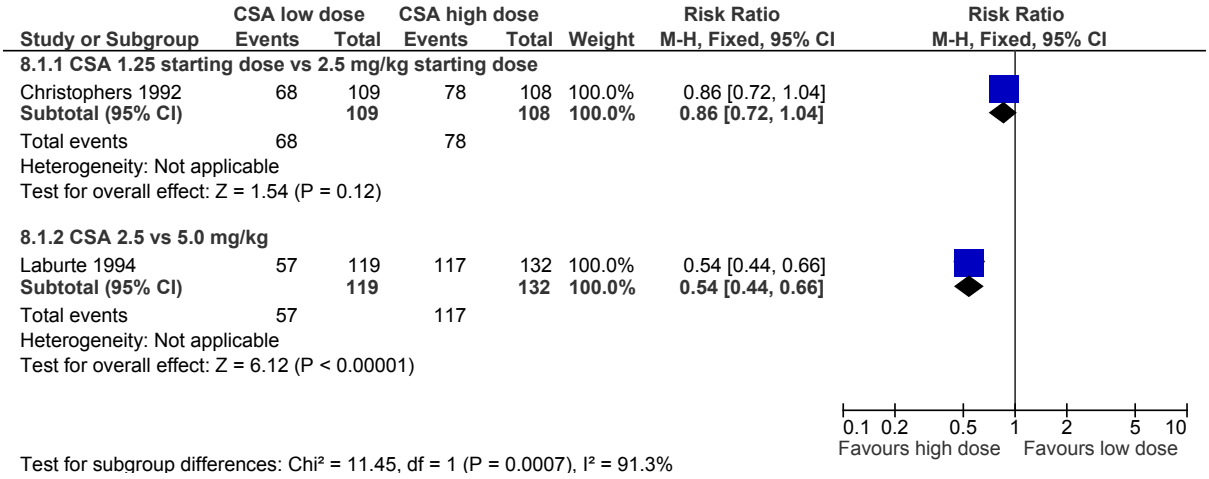


Figure 250: Elevated creatinine at 12-36 weeks

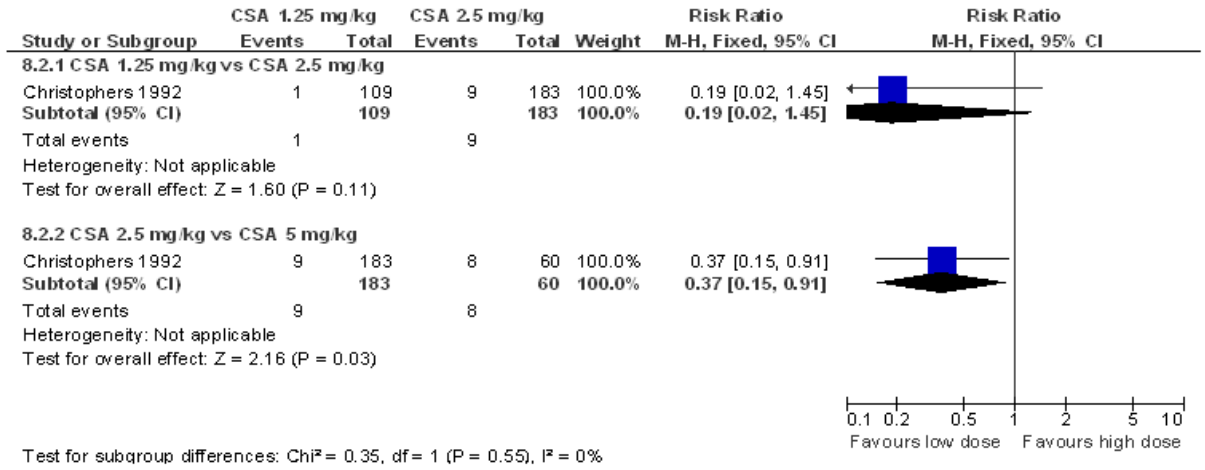


Figure 251: Hypertension at 12-36 weeks

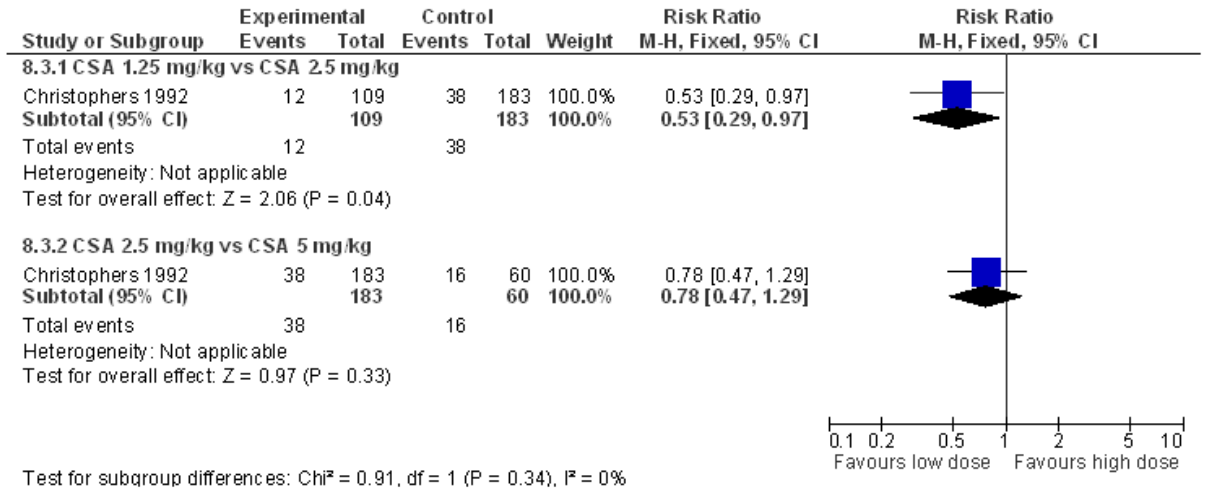
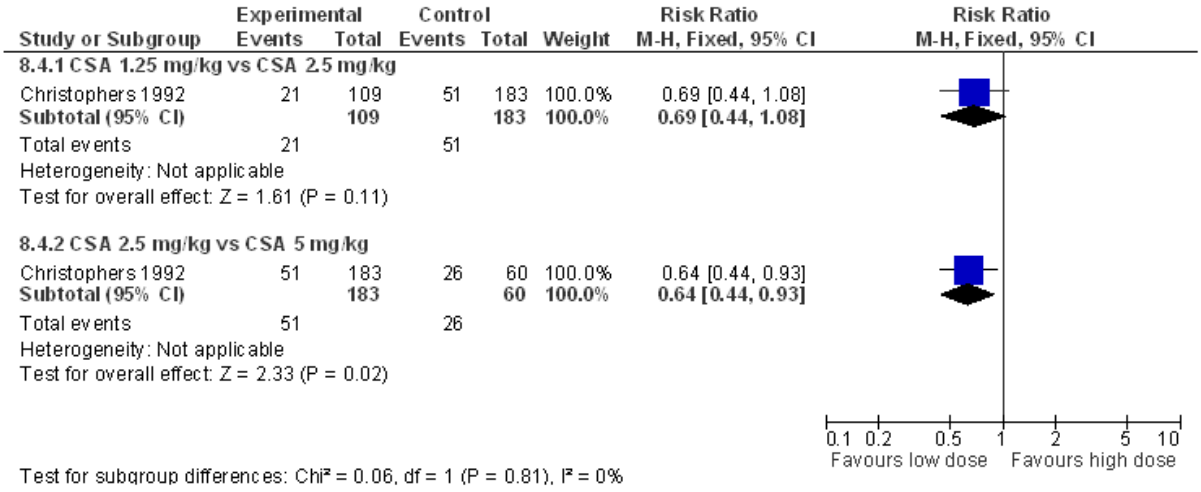


Figure 252: Elevated uric acid at 12-36 weeks



J.7.8 Ciclosporin vs placebo for maintenance of remission

Figure 253: PASI75 at 24 weeks

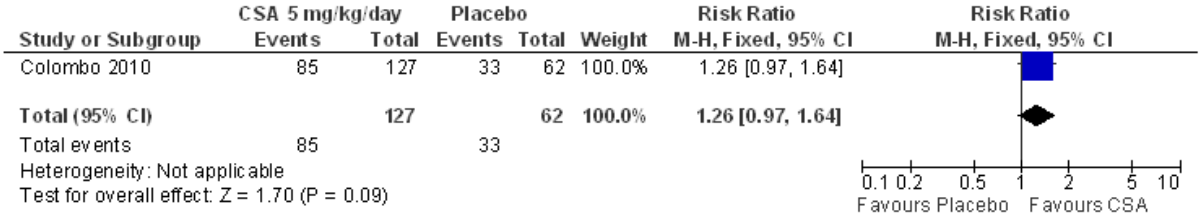


Figure 254: Final PASI at 24 weeks

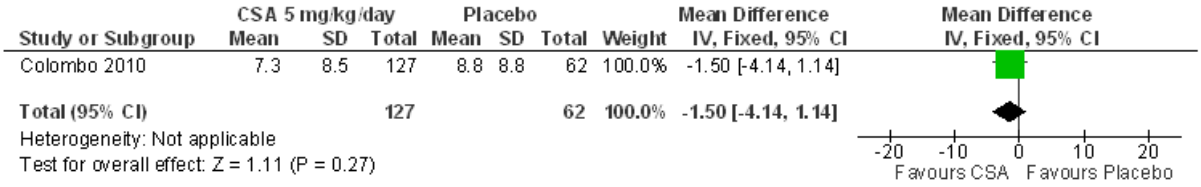


Figure 255: Maintaining at least mild psoriasis after indiction of PASI75 at 12 weeks

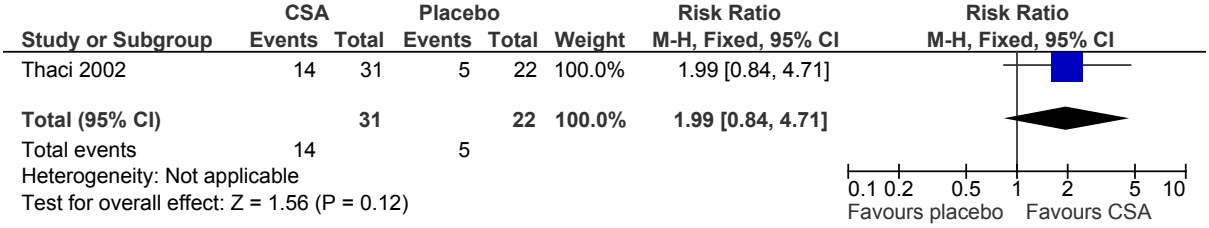


Figure 256: Time to relapse at 12-24 weeks

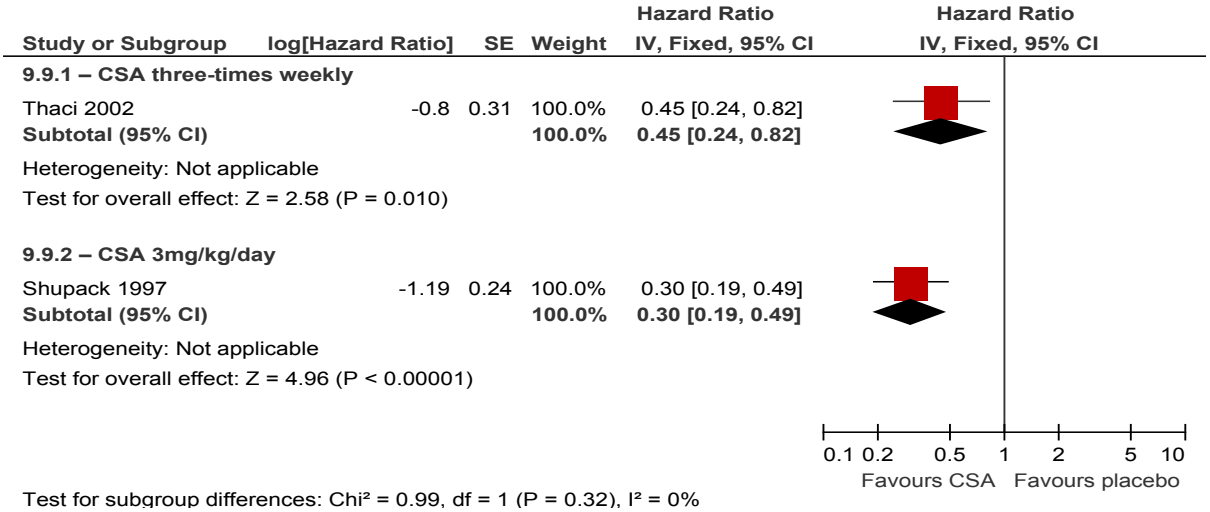


Figure 257: Mean time to relapse at 4 months

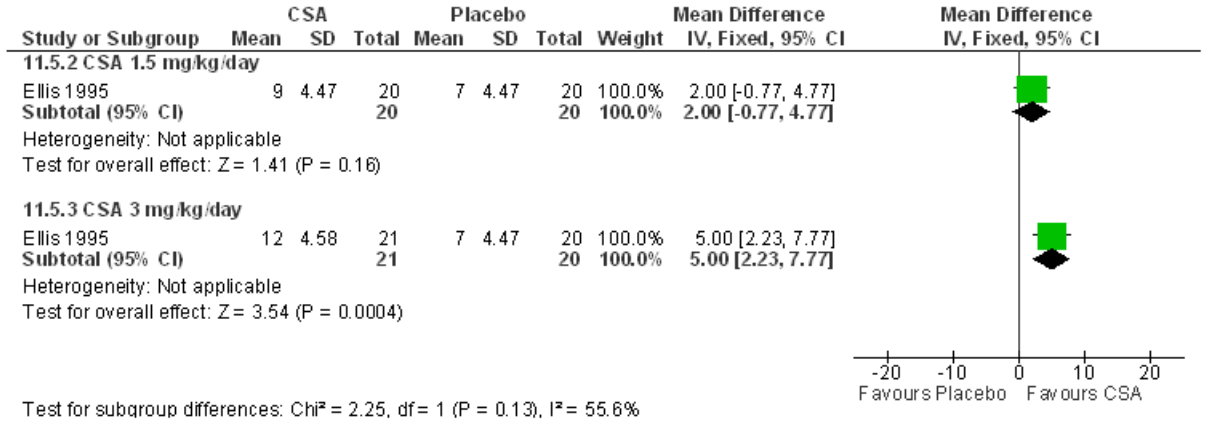


Figure 258: Relapse rate at 4 months

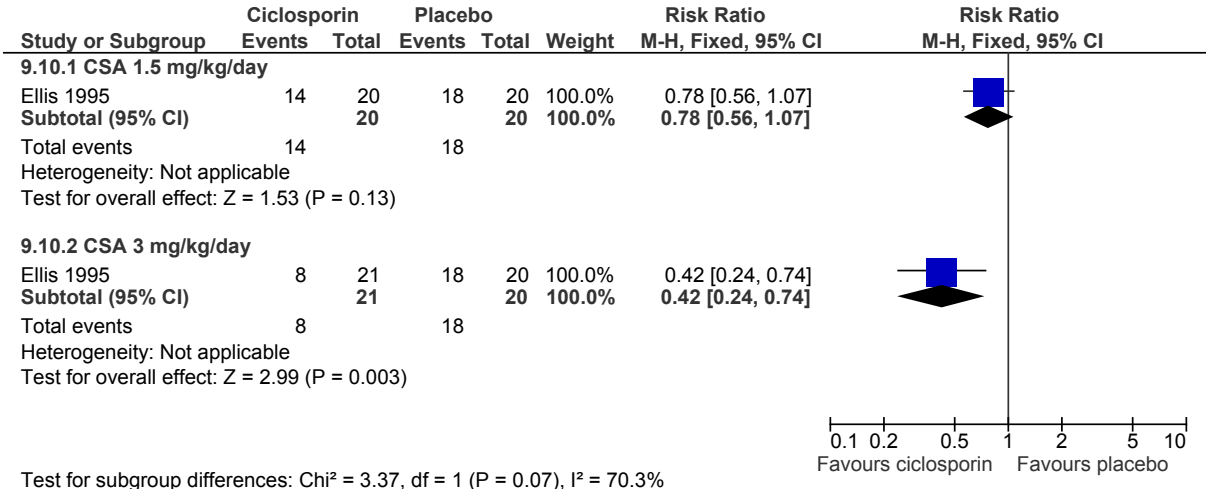


Figure 259: Relapse rate at 24 weeks - weekend only dosing

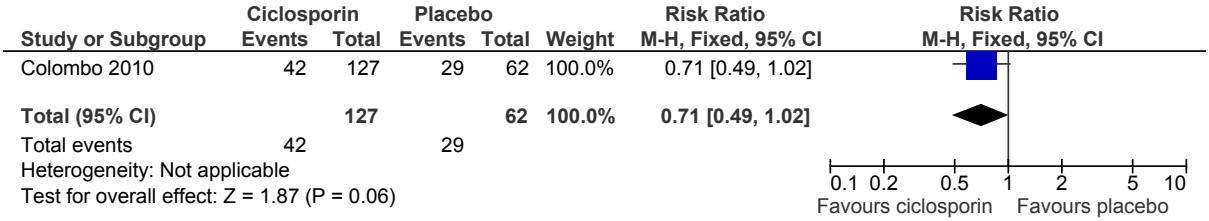


Figure 260: Withdrawal due to toxicity at 24 weeks

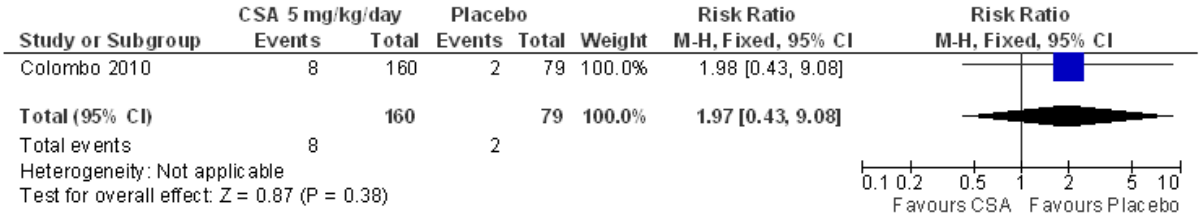


Figure 261: Severe adverse events at 24 weeks

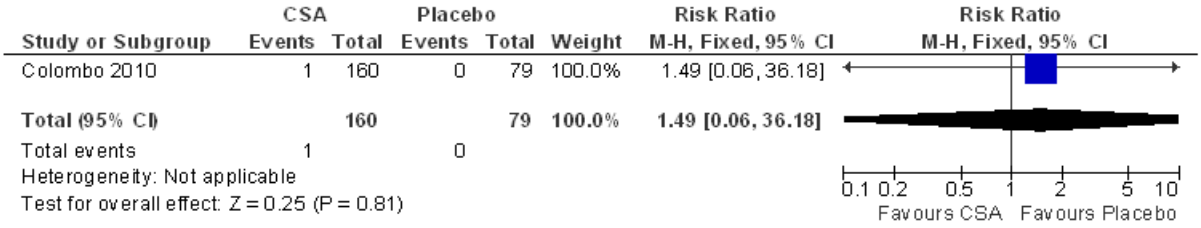
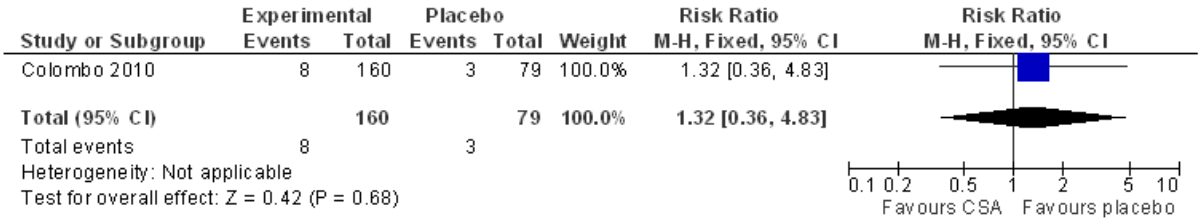


Figure 262: Elevated serum creatinine at 12 weeks



J.7.8.1 Intermittent (abrupt cessation) vs continuous ciclosporin for maintenance of remission

Figure 263: Clear/nearly clear (PASI90) at 9 months

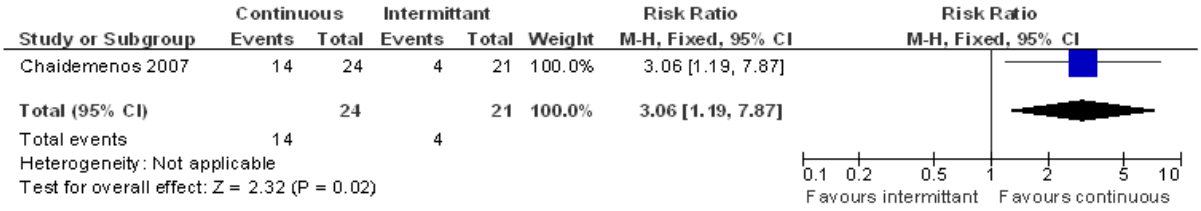


Figure 264: PASI75 at 9 months

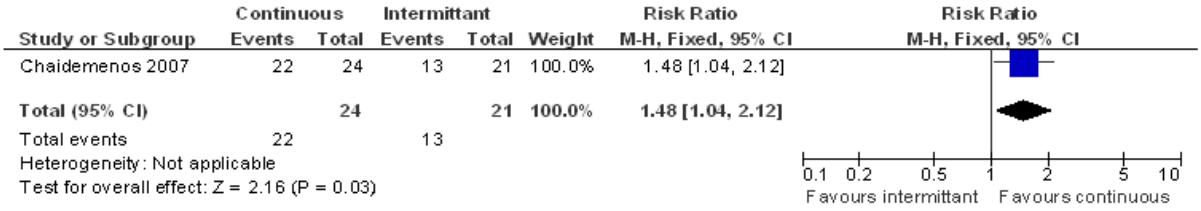


Figure 265: PASI50 at 9 months

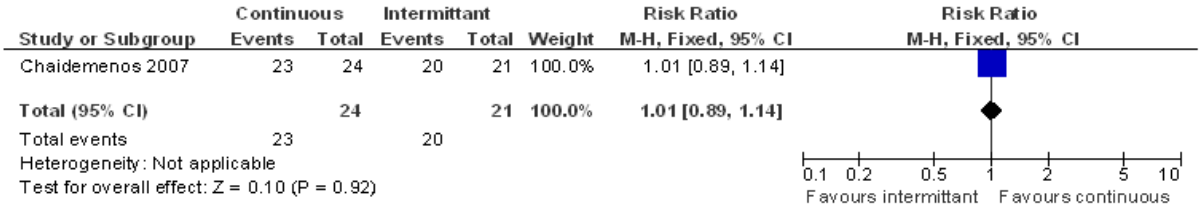


Figure 266: Time to relapse after a maximum follow-up of 1 year

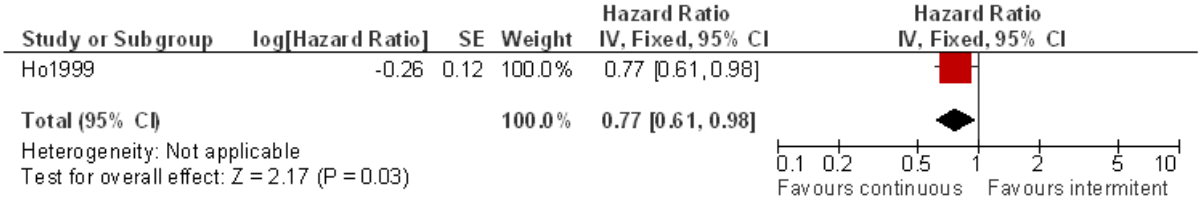


Figure 267: Increased serum creatinine at 9 months

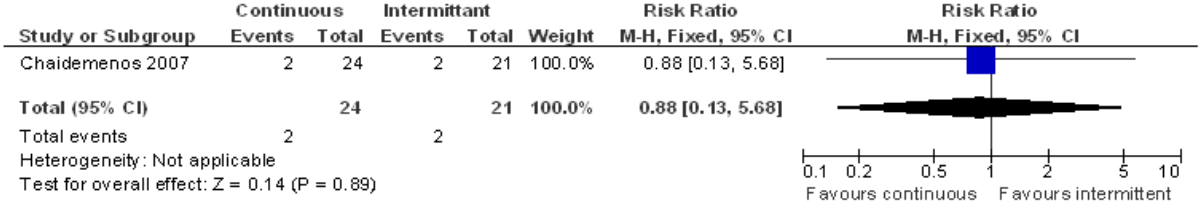
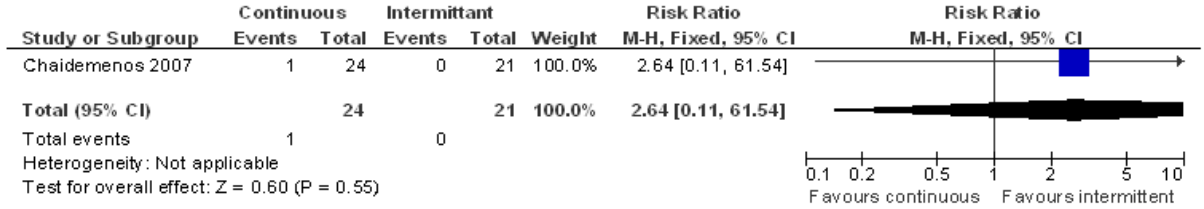


Figure 268: Hypertension at 9 months



J.7.8.2 Intermittent (taper to cessation) vs continuous ciclosporin for maintenance of remission

Figure 269: % change in PASI at 48 months

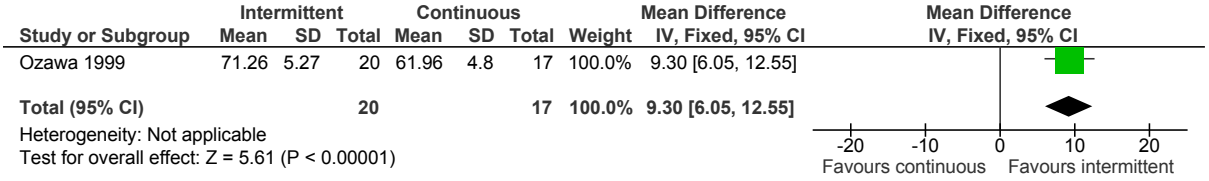


Figure 270: Final PASI at 48 months

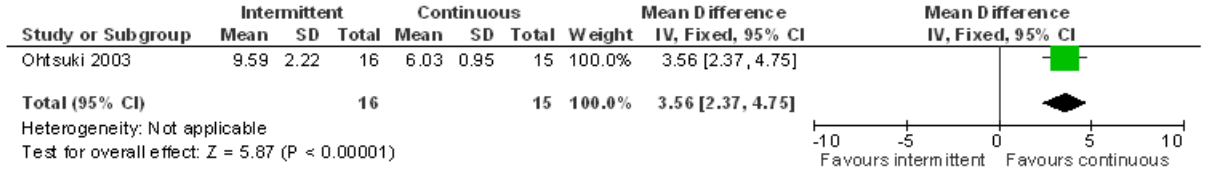


Figure 271: Withdrawal due to toxicity at 48 months

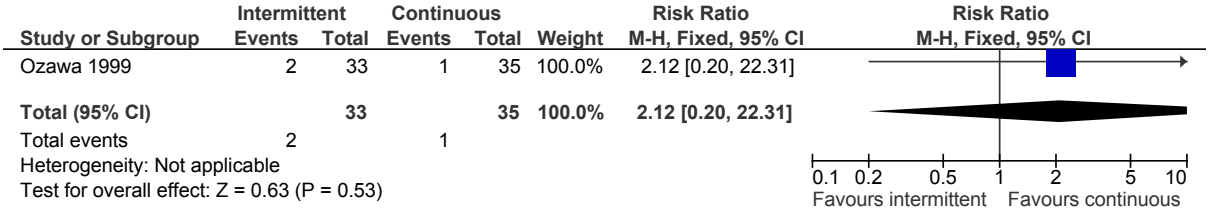


Figure 272: Hypertension at 1 year

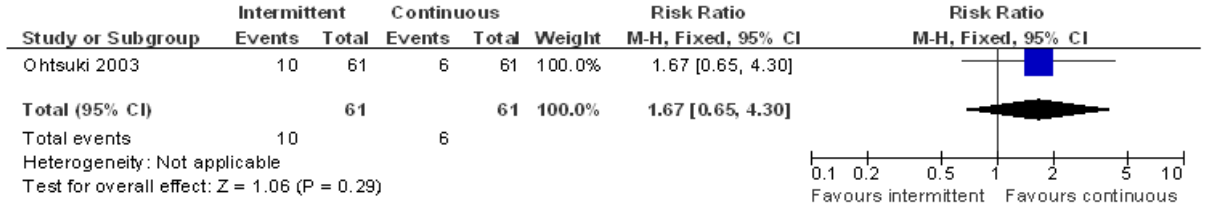


Figure 273: Increased creatinine at 1 year

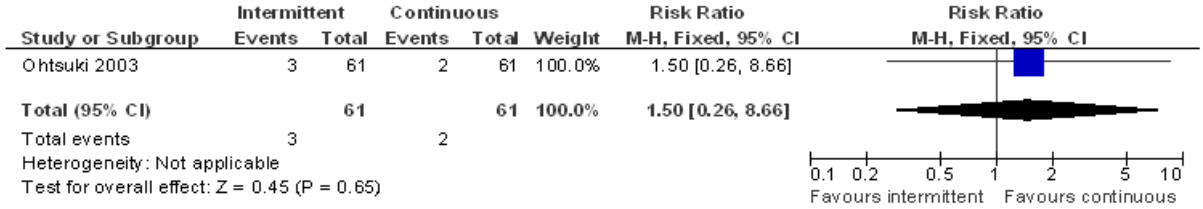


Figure 274: Hyperuricaemia at 1 year

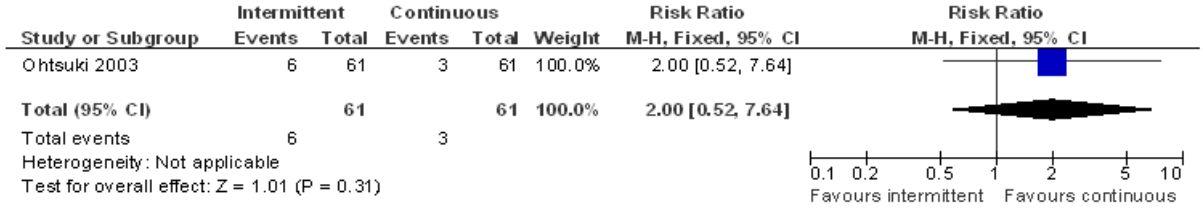
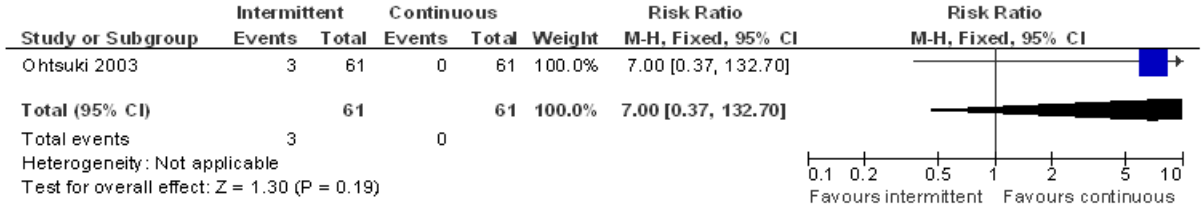


Figure 275: Increased liver enzymes at 1 year



J.7.9 Ciclosporin dosage comparisons for maintenance of remission

Figure 276: Severe adverse events at 18 months

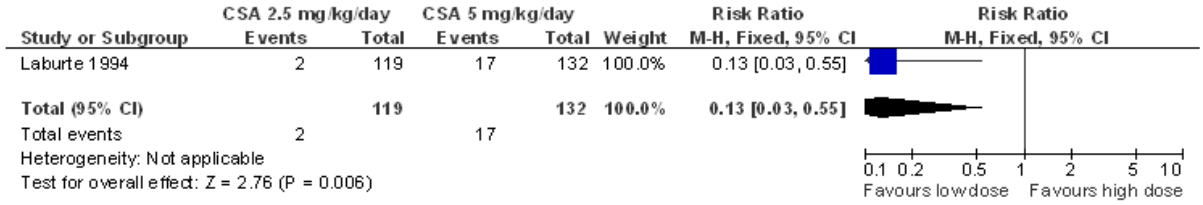


Figure 277: Hypertension at 18 months

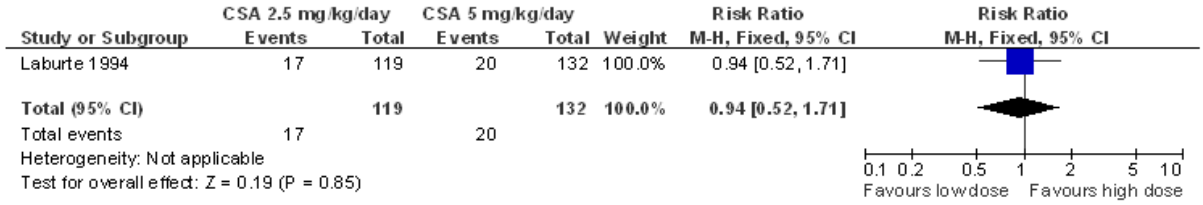


Figure 278: Elevated uric acid at 18 months

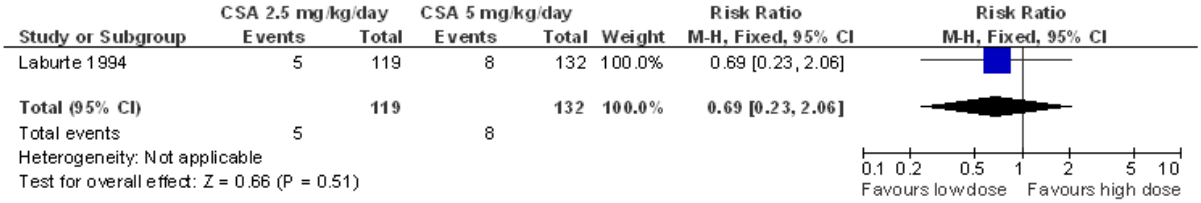
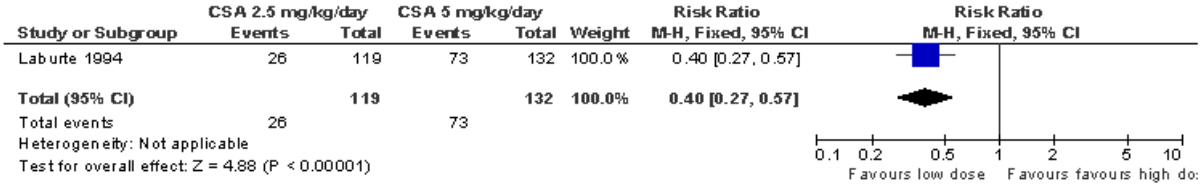


Figure 279: Elevated creatinine at 18 months



J.7.9.1 Ciclosporin vs placebo for induction of remission in palmoplantar pustulosis

Figure 280: Improvement at 4 weeks

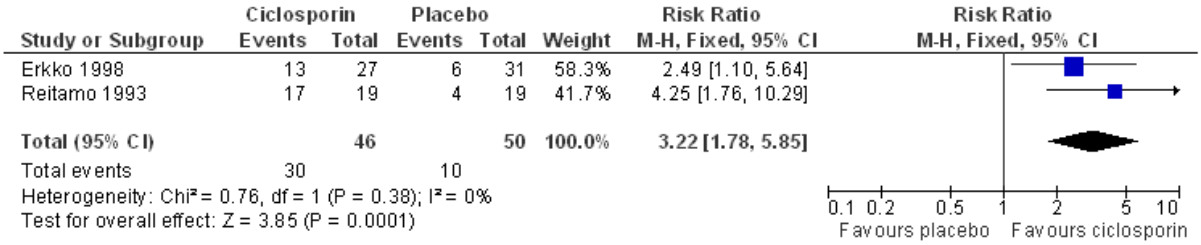


Figure 281: Hypertension at 1 month

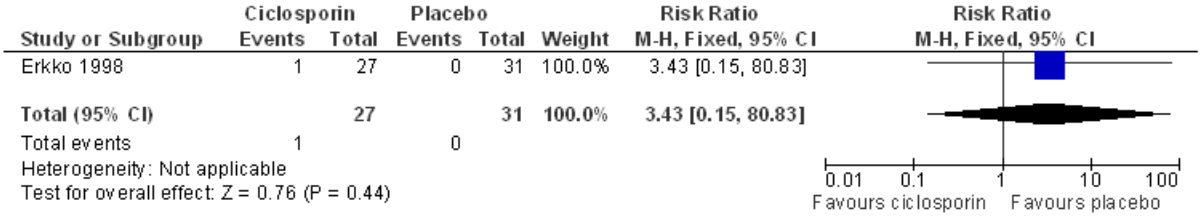


Figure 282: Hypertension at 12 months

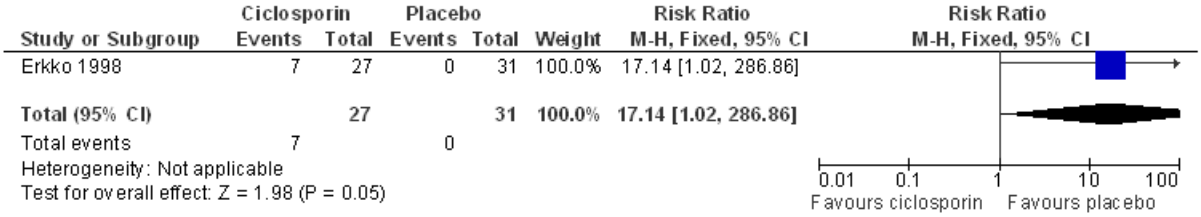


Figure 283: Increased serum creatinine at 12 months

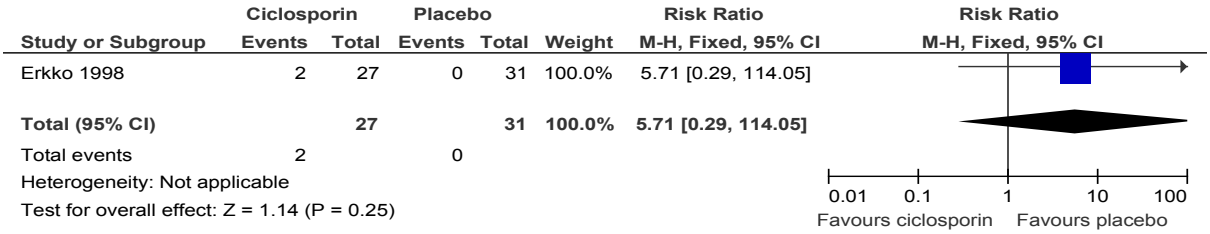


Figure 284: Improvement (open phase)

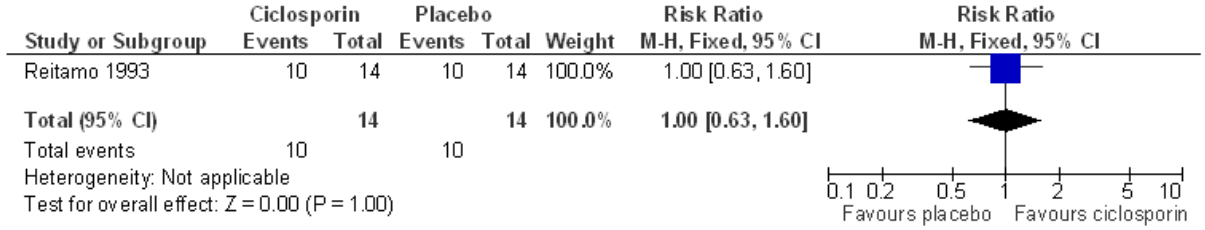


Figure 285: Relapse rate (open phase)

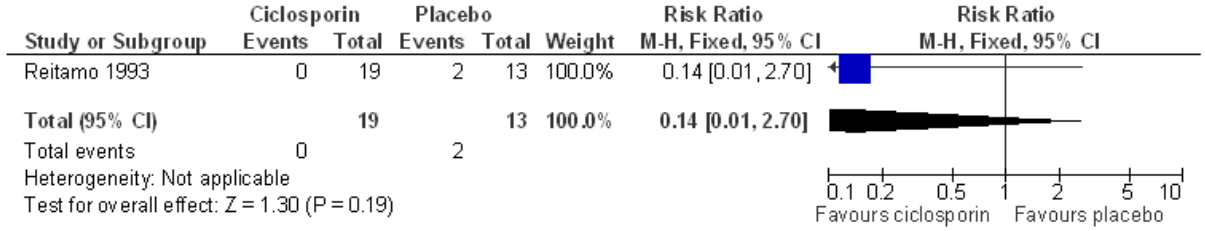


Figure 286: Relapse rate (withdrawal phase)

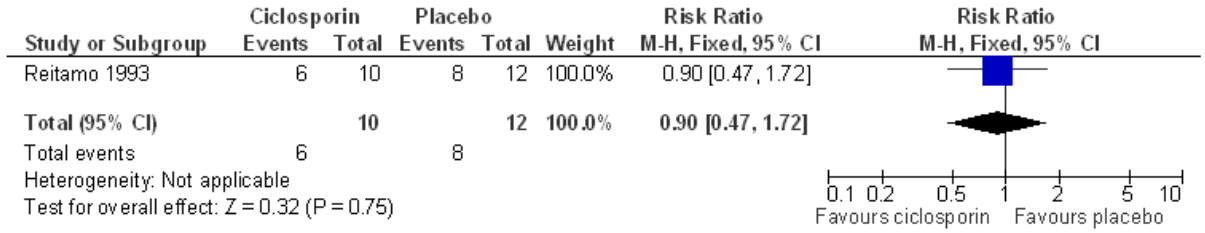


Figure 287: Gamma-glutamyl transferase vs biopsy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Paramsothy 1988	2	3	4	5	0.33 [0.04, 0.78]	0.63 [0.24, 0.91]

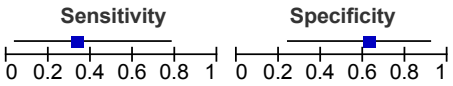


Figure 288: Liver scintigraphy vs biopsy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Geronemus 1982	4	6	3	11	0.57 [0.18, 0.90]	0.65 [0.38, 0.86]
McHenry 1992	5	15	1	66	0.83 [0.36, 1.00]	0.81 [0.71, 0.89]
Mitchell 1987	6	10	6	27	0.50 [0.21, 0.79]	0.73 [0.56, 0.86]

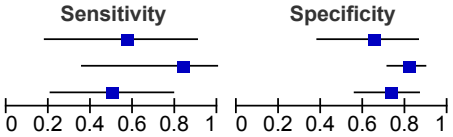
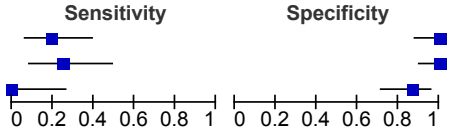


Figure 289: Ultrasound vs biopsy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Coulson 1987	5	0	21	28	0.19 [0.07, 0.39]	1.00 [0.88, 1.00]
Coulson 1987 - portal	5	0	15	34	0.25 [0.09, 0.49]	1.00 [0.90, 1.00]
Mitchell 1987	0	5	12	32	0.00 [0.00, 0.26]	0.86 [0.71, 0.95]



Note: all of the Coulson data are from the same population

Figure 290: PIIINP vs biopsy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Boffa 1996	17	24	4	42	0.81 [0.58, 0.95]	0.64 [0.51, 0.75]
Maurice 2005	15	49	9	102	0.63 [0.41, 0.81]	0.68 [0.59, 0.75]
Risteli 1988/Zachariae 89	19	1	6	46	0.76 [0.55, 0.91]	0.98 [0.89, 1.00]
Zachariae 2001	4	2	0	63	1.00 [0.40, 1.00]	0.97 [0.89, 1.00]

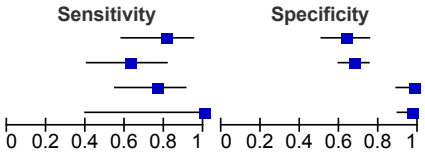


Figure 291: Fibrotest vs biopsy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berends 2007	5	7	1	11	0.83 [0.36, 1.00]	0.61 [0.36, 0.83]

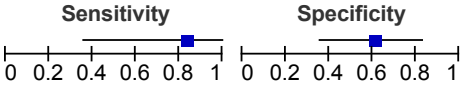
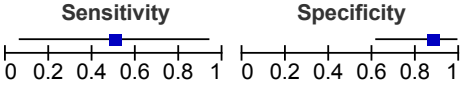


Figure 292: Fibroscan vs biopsy

Study	TP	FP	FN	TN	Sensitivity	Specificity
Berends 2007	2	2	2	14	0.50 [0.07, 0.93]	0.88 [0.62, 0.98]



Note: there is uncertainty about the accuracy of the values for TP, FP, FN and TN for this test

J.8 Sequencing of biologic therapy

The majority of the data presented in the forest plots below are derived from observational studies and must be interpreted with caution. Note also that all observational study data have been considered individually and the forest plots do not represent combined data from multiple studies.

J.8.1 Previous biologic vs no previous biologic

J.8.1.1 Etanercept

Figure 293: Clear/nearly clear (PASI 90) at week 12

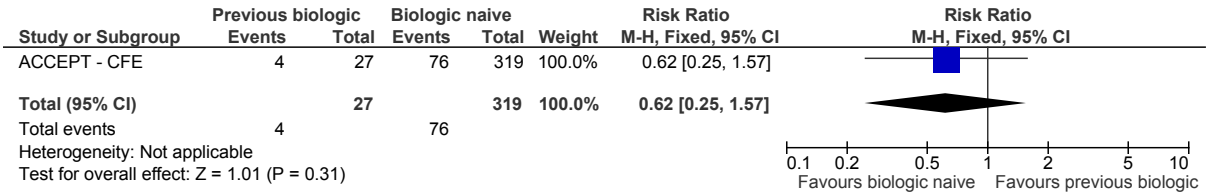


Figure 294: Clear/nearly clear (PGA) at week 12

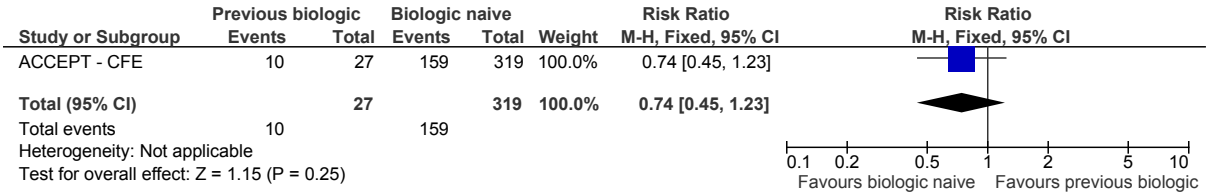


Figure 295: PASI75 (week 12)

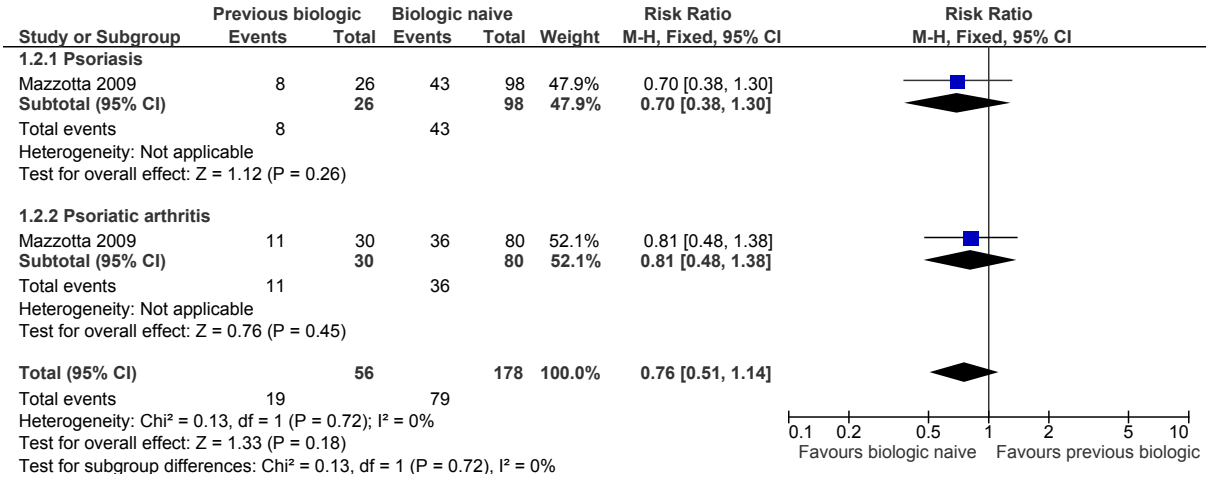


Figure 296: PASI75 (week 12)

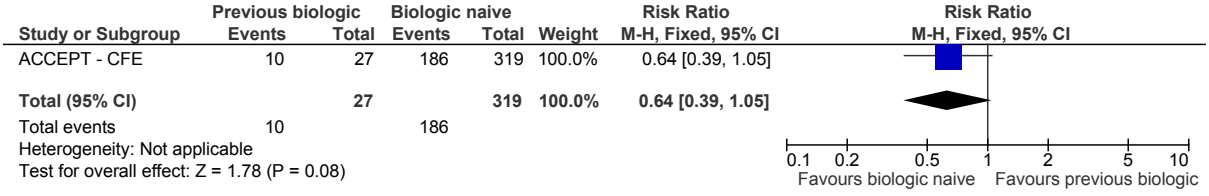


Figure 297: PASI75 at week 24

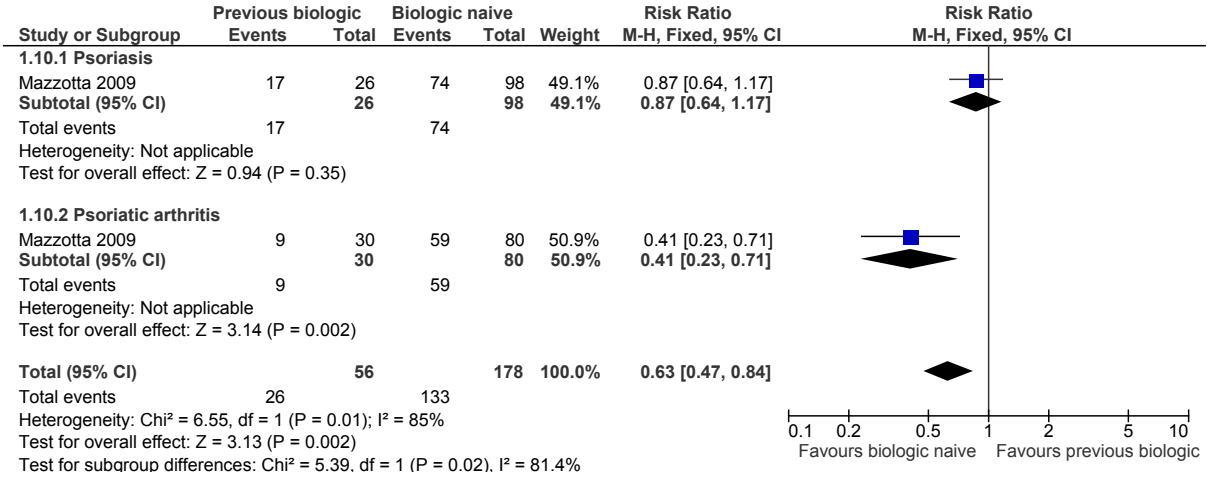


Figure 298: PASI50 (week 12)

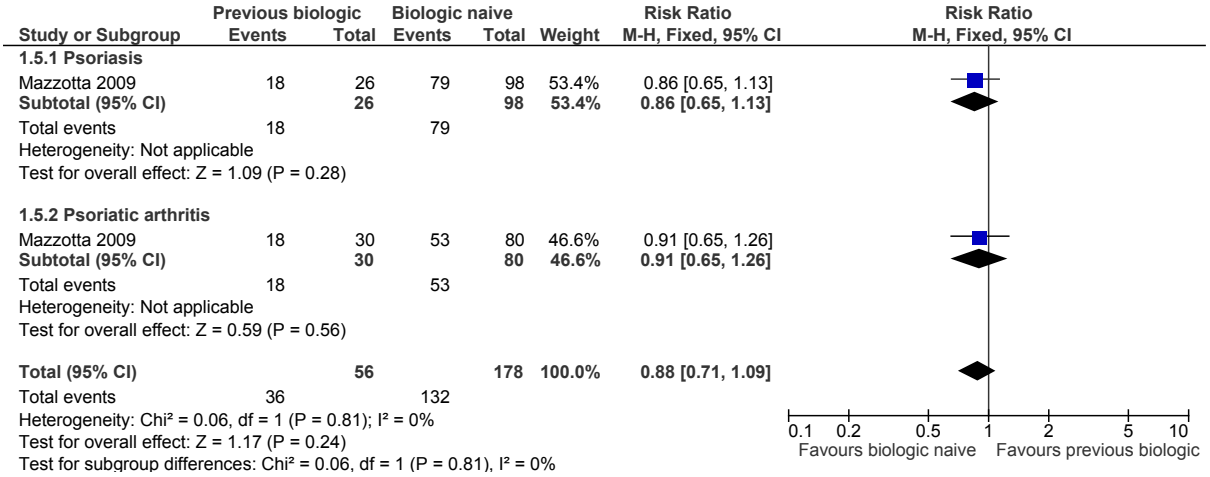


Figure 299: PASI50 (week 12)

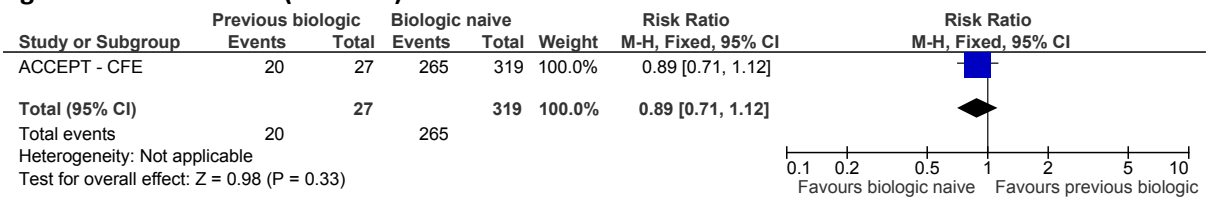


Figure 300: PASI 50 (week 24)

Study or Subgroup	Previous biologic Events	Total	Biologic naive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Psoriasis						
Mazzotta 2009	18	26	88	98	47.8%	0.77 [0.59, 1.00]
Subtotal (95% CI)		**26**		**98**	**47.8%**	**0.77 [0.59, 1.00]**
Total events	18		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
1.6.2 Psoriatic arthritis						
Mazzotta 2009	14	30	74	80	52.2%	0.50 [0.34, 0.74]
Subtotal (95% CI)		**30**		**80**	**52.2%**	**0.50 [0.34, 0.74]**
Total events	14		74			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.46 (P = 0.0005)						
Total (95% CI)		**56**		**178**	**100.0%**	**0.63 [0.50, 0.79]**
Total events	32		162			
Heterogeneity: Chi² = 3.47, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 3.94 (P < 0.0001)						
Test for subgroup differences: Chi² = 3.14, df = 1 (P = 0.08), I² = 68.1%						

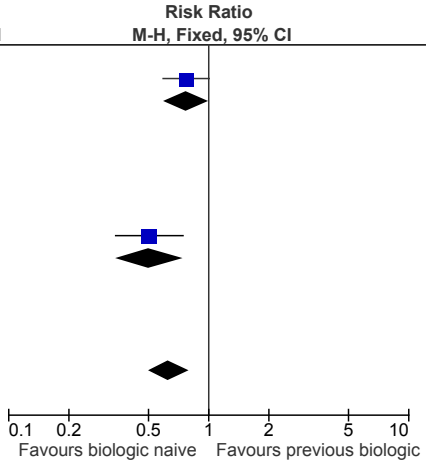


Figure 301: % improvement in PASI (week 12)

Study or Subgroup	Previous biologic Mean	SD	Total	Biologic naive Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
ACCEPT - CFE	65.55	25.87	27	72.59	25.953	311	100.0%	-7.04 [-17.22, 3.14]
Total (95% CI)			**27**			**311**	**100.0%**	**-7.04 [-17.22, 3.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.18)								

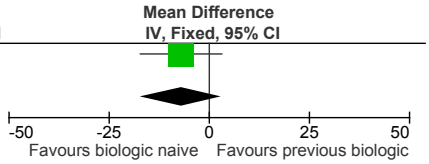


Figure 302: Final PASI (week 12)

Study or Subgroup	Previous biologic Mean	SD	Total	Biologic naive Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.15.1 Psoriasis								
Mazzotta 2009	5.4	3.8	26	4.9	4	98	35.6%	0.50 [-1.16, 2.16]
Subtotal (95% CI)			**26**			**98**	**35.6%**	**0.50 [-1.16, 2.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.15.2 Psoriatic arthritis								
Mazzotta 2009	2.9	2.6	30	2.9	3.7	80	64.4%	0.00 [-1.23, 1.23]
Subtotal (95% CI)			**30**			**80**	**64.4%**	**0.00 [-1.23, 1.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**56**			**178**	**100.0%**	**0.18 [-0.81, 1.17]**
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%								

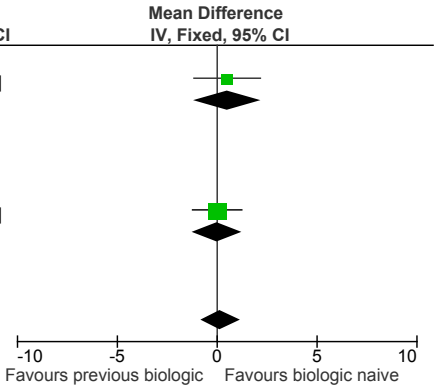
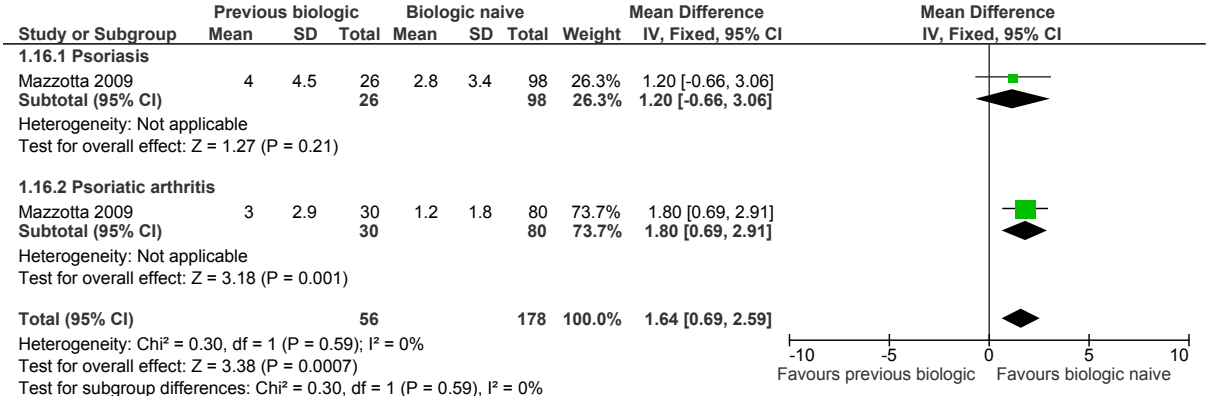
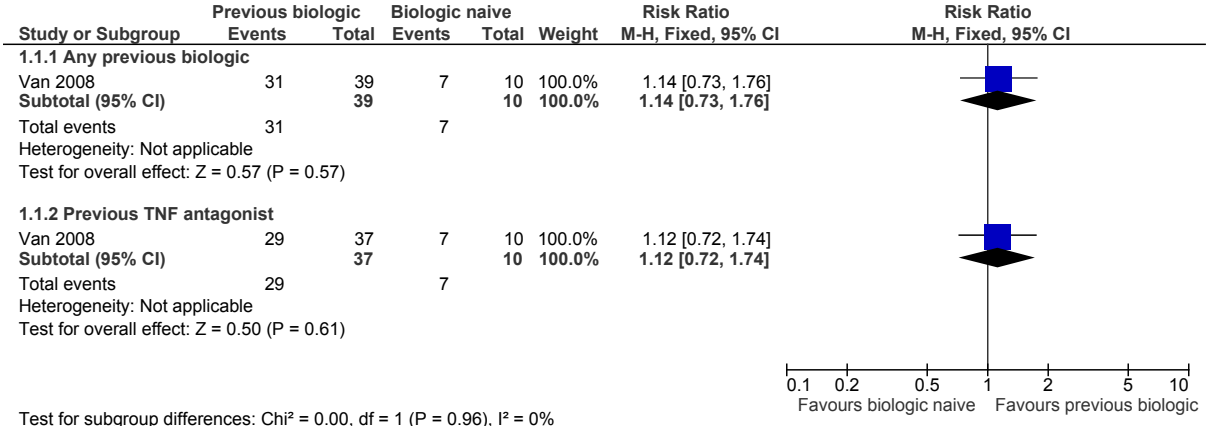


Figure 303: Final PASI (week 24)



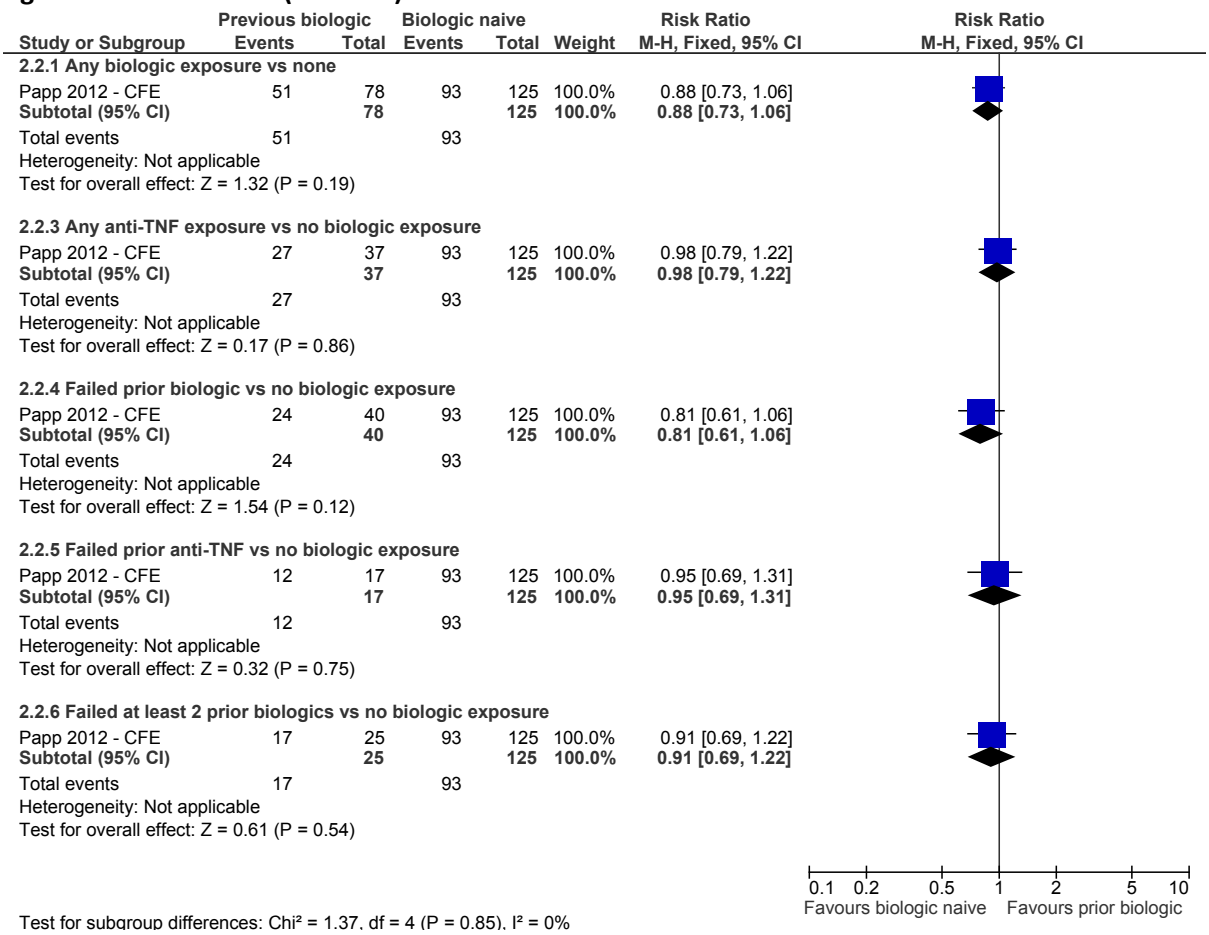
J.8.1.2 Adalimumab

Figure 304: Clear/nearly clear at 12 months



Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

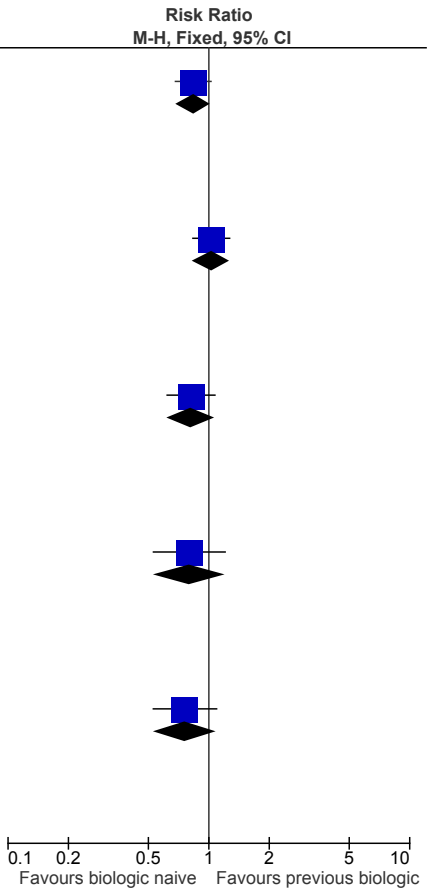
Figure 305: PASI75 (week 16)



Test for subgroup differences: Chi² = 1.37, df = 4 (P = 0.85), I² = 0%

Figure 306: PASI75 (week 24)

Study or Subgroup	Previous biologic Events	Total	Biologic naive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Any biologic exposure vs none						
Papp 2012 - CFE	48	78	92	125	100.0%	0.84 [0.68, 1.03]
Subtotal (95% CI)		**78**		**125**	**100.0%**	**0.84 [0.68, 1.03]**
Total events	48		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
2.6.2 Any anti-TNF exposure vs no biologic exposure						
Papp 2012 - CFE	28	37	92	125	100.0%	1.03 [0.83, 1.27]
Subtotal (95% CI)		**37**		**125**	**100.0%**	**1.03 [0.83, 1.27]**
Total events	28		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.6.3 Failed prior biologic vs no biologic exposure						
Papp 2012 - CFE	24	40	92	125	100.0%	0.82 [0.62, 1.07]
Subtotal (95% CI)		**40**		**125**	**100.0%**	**0.82 [0.62, 1.07]**
Total events	24		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
2.6.4 Failed prior anti-TNF vs no biologic exposure						
Papp 2012 - CFE	10	17	92	125	100.0%	0.80 [0.53, 1.21]
Subtotal (95% CI)		**17**		**125**	**100.0%**	**0.80 [0.53, 1.21]**
Total events	10		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
2.6.5 Failed at least 2 prior biologics vs no biologic exposure						
Papp 2012 - CFE	14	25	92	125	100.0%	0.76 [0.53, 1.09]
Subtotal (95% CI)		**25**		**125**	**100.0%**	**0.76 [0.53, 1.09]**
Total events	14		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						

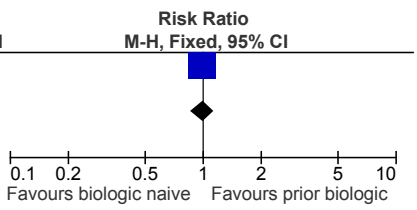


Test for subgroup differences: Chi² = 3.45, df = 4 (P = 0.48), I² = 0%

J.8.1.3 Infliximab

Figure 307: PASI75 (week 10)

Study or Subgroup	Prior biologic Events	Total	No prior biologic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menter 2007	68	94	389	533	100.0%	0.99 [0.87, 1.13]
Total (95% CI)		**94**		**533**	**100.0%**	**0.99 [0.87, 1.13]**
Total events	68		389			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						



J.8.1.4 Ustekinumab

Figure 308: Clear/nearly clear (PASI90) at weeks 12, 24 and 52

Study or Subgroup	Previous biologic Events	Total	Biologic naive Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Week 12 (ITT)					
ACCEPT - CFE	10	36	221	519	0.65 [0.38, 1.12]
PHOENIX1 - CFE	75	212	125	299	0.85 [0.68, 1.06]
PHOENIX2 - CFE	94	250	288	570	0.74 [0.62, 0.89]
3.1.2 Week 24 (ACA)					
PHOENIX1 - CFE	114	207	182	290	0.88 [0.75, 1.02]
PHOENIX2 - CFE	113	242	329	558	0.79 [0.68, 0.92]
3.1.3 Week 52 (ACA)					
PHOENIX1 - CFE	39	59	66	103	1.03 [0.82, 1.30]
PHOENIX2 - CFE	86	148	276	389	0.82 [0.70, 0.95]

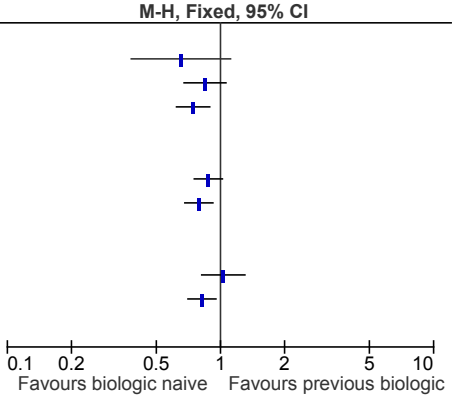


Figure 309: Clear/nearly clear (PGA) at weeks 12, 24 and 52

Study or Subgroup	Previous biologic Events	Total	Biologic naive Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Week 12 (ITT)					
ACCEPT - CFE	19	36	362	519	0.76 [0.55, 1.04]
PHOENIX1 - CFE	122	212	190	299	0.91 [0.78, 1.05]
PHOENIX2 - CFE	162	250	418	570	0.88 [0.80, 0.98]
3.2.2 Week 24 (ACA)					
PHOENIX1 - CFE	137	207	213	290	0.90 [0.80, 1.02]
PHOENIX2 - CFE	159	242	419	558	0.87 [0.79, 0.97]
3.2.3 Week 52 (ACA)					
PHOENIX1 - CFE	43	59	72	103	1.04 [0.85, 1.27]
PHOENIX2 - CFE	98	148	291	389	0.89 [0.78, 1.01]

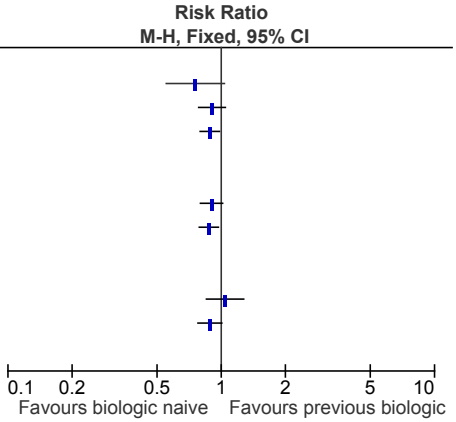


Figure 310: PASI75 at weeks 12, 24 and 52

Study or Subgroup	Favours biologic naive Events	Total	Biologic naive Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Week 12 (ITT)					
ACCEPT - CFE	20	36	377	519	0.76 [0.57, 1.03]
PHOENIX1 - CFE	128	212	213	299	0.85 [0.74, 0.97]
PHOENIX2 - CFE	158	250	426	570	0.85 [0.76, 0.94]
3.3.2 Week 24 (ACA)					
PHOENIX1 - CFE	155	207	245	290	0.89 [0.81, 0.97]
PHOENIX2 - CFE	181	242	446	558	0.94 [0.86, 1.02]
3.3.3 Week 28 (ACA)					
Papp 2008	209	307	380	513	0.92 [0.84, 1.01]
3.3.4 Week 52 (ACA)					
PHOENIX1 - CFE	51	59	93	103	0.96 [0.85, 1.08]
PHOENIX2 - CFE	127	148	360	389	0.93 [0.86, 1.00]

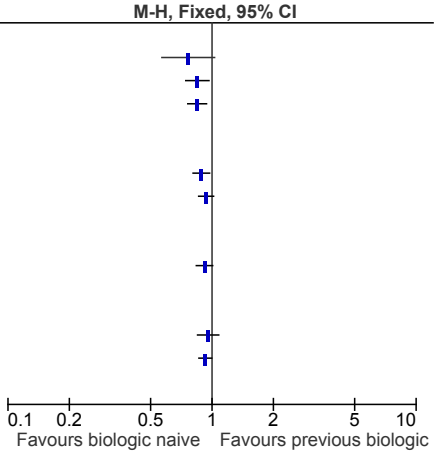


Figure 311: PASI75 (week 16)

Study or Subgroup	Previous biologic Events	Total	Biologic naive Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.26.2 Any biologic exposure vs none					
Laws 2011 - CFE	64	106	16	21	0.79 [0.60, 1.05]
3.26.7 None or one prior biologic vs 2-4 prior biologics					
Laws 2011 - CFE	45	79	35	48	0.78 [0.60, 1.01]

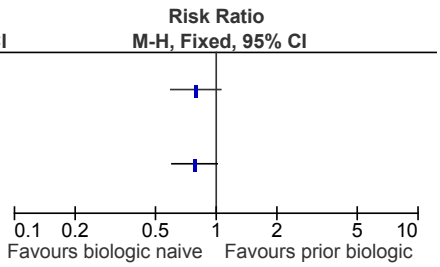


Figure 312: PASI50 (weeks 12, 24 and 52)

Study or Subgroup	Previous biologic Events	Total	Biologic naive Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Week 12 (ITT)					
ACCEPT - CFE	28	36	473	519	0.85 [0.72, 1.02]
PHOENIX1 - CFE	171	212	262	299	0.92 [0.85, 1.00]
PHOENIX2 - CFE	213	250	496	570	0.98 [0.92, 1.04]
3.6.2 Week 24 (ACA)					
PHOENIX1 - CFE	186	207	275	290	0.95 [0.90, 1.00]
PHOENIX2 - CFE	225	242	517	558	1.00 [0.96, 1.05]
3.6.3 Week 52 (ACA)					
PHOENIX1 - CFE	57	59	101	103	0.99 [0.93, 1.04]
PHOENIX2 - CFE	146	148	386	389	0.99 [0.97, 1.02]

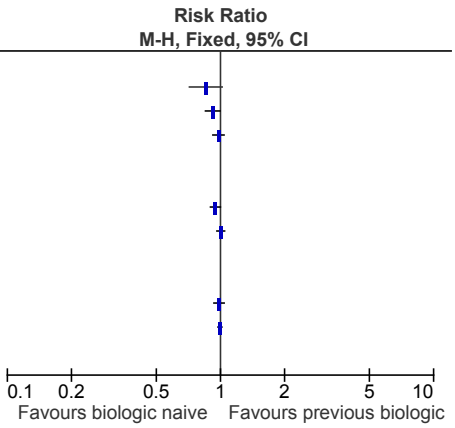


Figure 313: % improvement in PASI (weeks 12, 24 and 52)

Study or Subgroup	Previous biologic Mean	SD	Total	Biologic naive Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.7.1 Week 12 (ITT)							
ACCEPT - CFE	68.3	31.676	35	82.05	20.799	508	-13.75 [-24.40, -3.10]
PHOENIX1 - CFE	73.14	27.856	208	78.69	23.338	298	-5.55 [-10.17, -0.93]
PHOENIX2 - CFE	76.61	23.638	248	80.8	24.558	564	-4.19 [-7.76, -0.62]
3.7.2 Week 24 (ACA)							
PHOENIX1 - CFE	82.59	23.52	207	86.96	19.36	290	-4.37 [-8.27, -0.47]
PHOENIX2 - CFE	82.38	21.478	123	85.07	21.64	283	-2.69 [-7.25, 1.87]
3.7.3 Week 52 (ACA)							
PHOENIX1 - CFE	89.45	14.73	59	90.15	14.62	103	-0.70 [-5.40, 4.00]
PHOENIX2 - CFE	88.12	14.464	148	91.86	12.67	389	-3.74 [-6.39, -1.09]

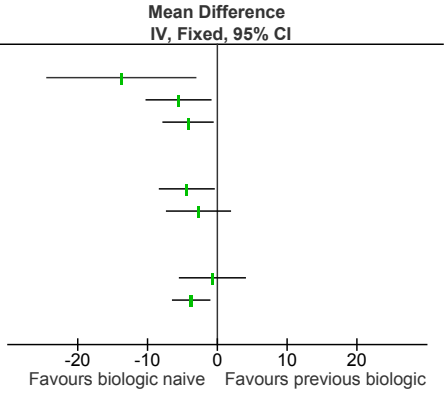
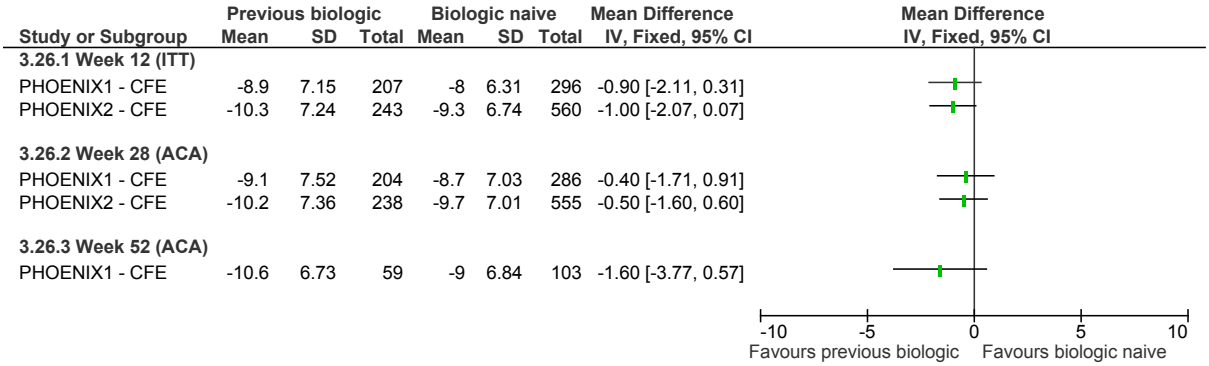


Figure 314: Change in DLQI (weeks 12, 24 and 52)



J.8.2 Adalimumab as a first TNF antagonist vs adalimumab following discontinuation of a previous TNF antagonist

Figure 315: Clear/nearly clear (PASI90; 16 weeks)

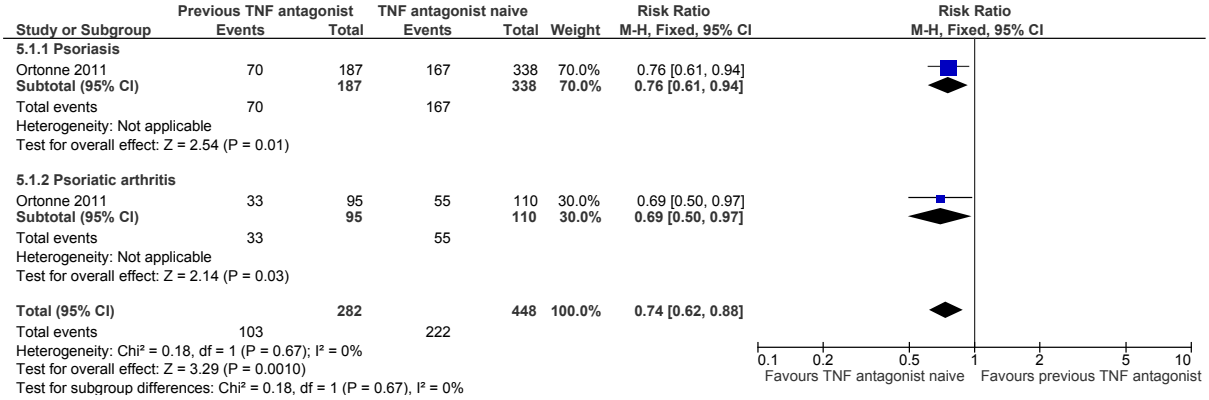


Figure 316: Clear/nearly clear (PGA; 16 weeks)

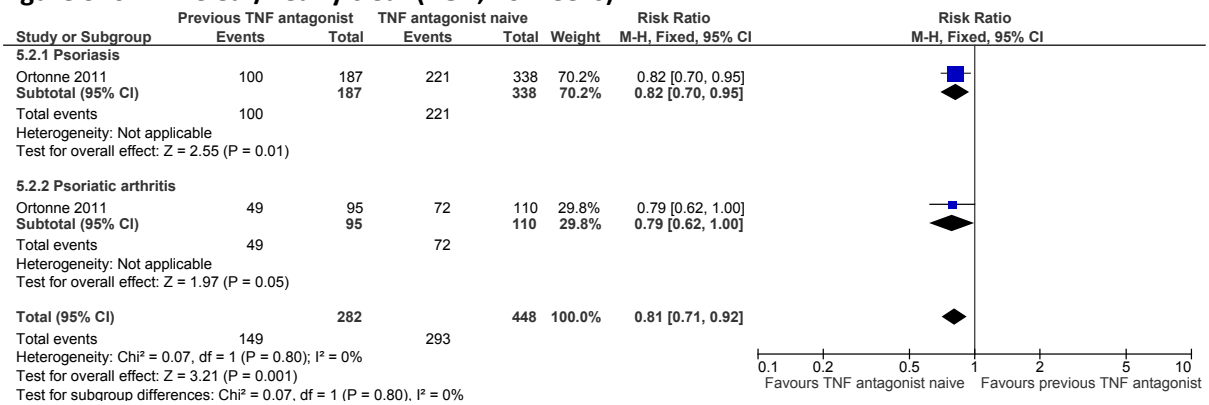


Figure 317: Clear/nearly clear (PGA; week 16)

Study or Subgroup	Failed etanercept Events	Total	Failed conventional Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strober 2011	40	77	39	66	100.0%	0.88 [0.66, 1.18]
Total (95% CI)		**77**		**66**	**100.0%**	**0.88 [0.66, 1.18]**
Total events	40		39			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)

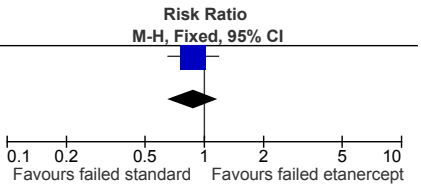


Figure 318: Clear/nearly clear (PGA; week 16)

Study or Subgroup	Failed etanercept Events	Total	Failed conventional Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 Primary non-responder						
Strober 2011-CFE	15	26	28	45	61.4%	0.93 [0.62, 1.38]
Subtotal (95% CI)		**26**		**45**	**61.4%**	**0.93 [0.62, 1.38]**
Total events	15		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

6.2.2 Secondary non-responder						
Strober 2011-CFE	27	58	9	23	38.6%	1.19 [0.67, 2.12]
Subtotal (95% CI)		**58**		**23**	**38.6%**	**1.19 [0.67, 2.12]**
Total events	27		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)

Total (95% CI)		**84**		**68**	**100.0%**	**1.03 [0.74, 1.44]**
Total events	42		37			

Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%

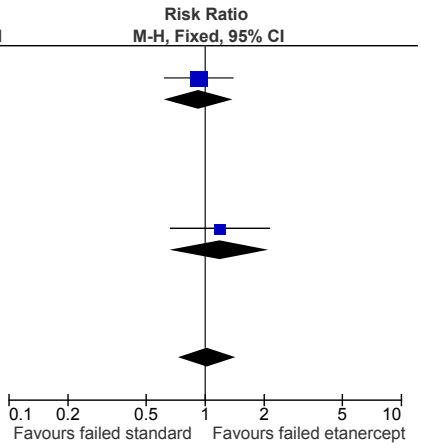


Figure 319: PASI75 (week 16)

Study or Subgroup	Previous TNF antagonist Events	Total	TNF antagonist naive Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Psoriasis						
Ortonne 2011	123	187	244	338	70.9%	0.91 [0.81, 1.03]
Subtotal (95% CI)		**187**		**338**	**70.9%**	**0.91 [0.81, 1.03]**
Total events	123		244			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)

2.2.2 Psoriatic arthritis						
Ortonne 2011	51	95	77	110	29.1%	0.77 [0.61, 0.96]
Subtotal (95% CI)		**95**		**110**	**29.1%**	**0.77 [0.61, 0.96]**
Total events	51		77			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.33 (P = 0.02)

Total (95% CI)		**282**		**448**	**100.0%**	**0.87 [0.78, 0.97]**
Total events	174		321			

Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Chi² = 1.76, df = 1 (P = 0.18), I² = 43.1%

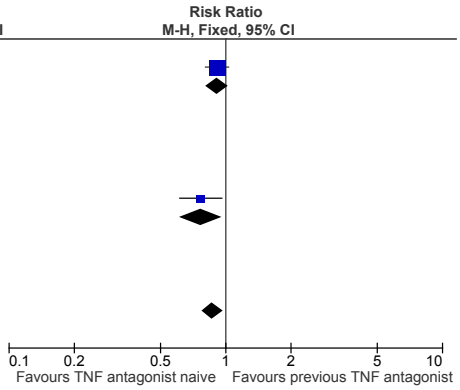


Figure 320: Withdrawal due to lack of efficacy at week 16

Study or Subgroup	Previous TNF antagonist Events	Total	TNF antagonist naive Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ortonne 2011	3	270	5	414	0.92 [0.22, 3.82]
Strober 2011	4	77	3	66	1.14 [0.27, 4.92]

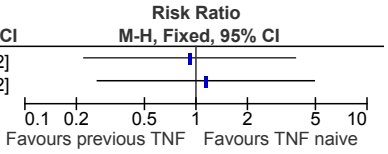


Figure 321: Withdrawal due to toxicity at week 16

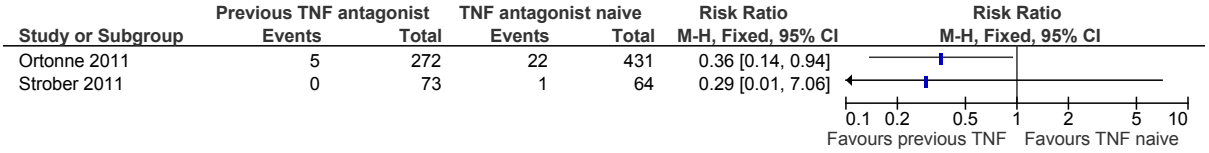
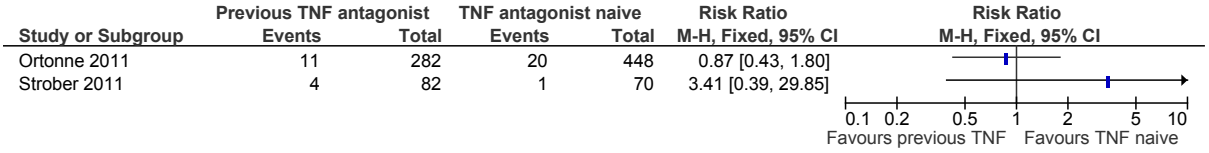
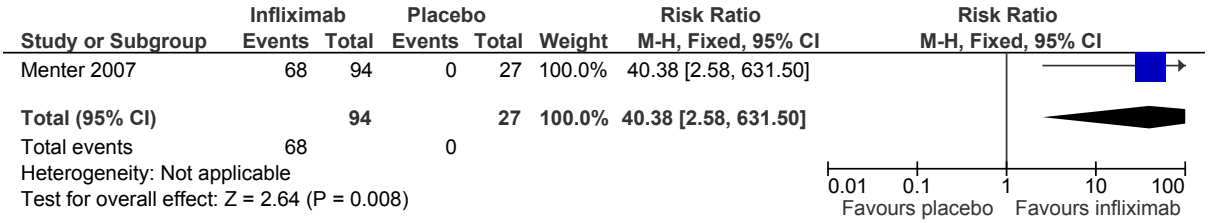


Figure 322: Serious adverse events after 16 weeks (plus 70 days post-treatment)



J.8.3 Infliximab vs placebo

Figure 323: PASI75 (week 10)



J.8.4 Ustekinumab vs placebo

Figure 324: Clear/nearly clear (PASI90; week 12)

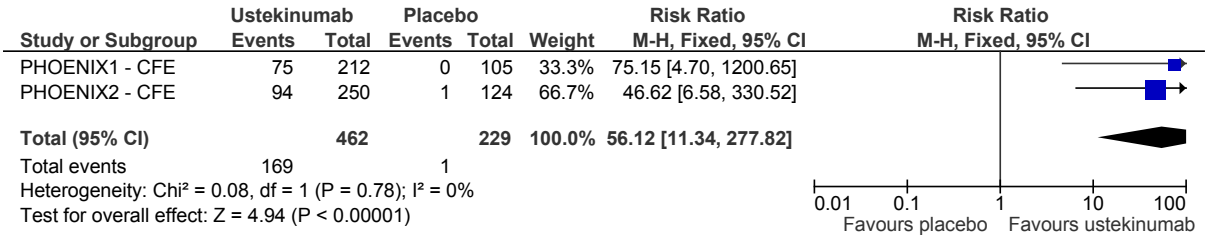


Figure 325: Clear/nearly clear (PGA; week 12)

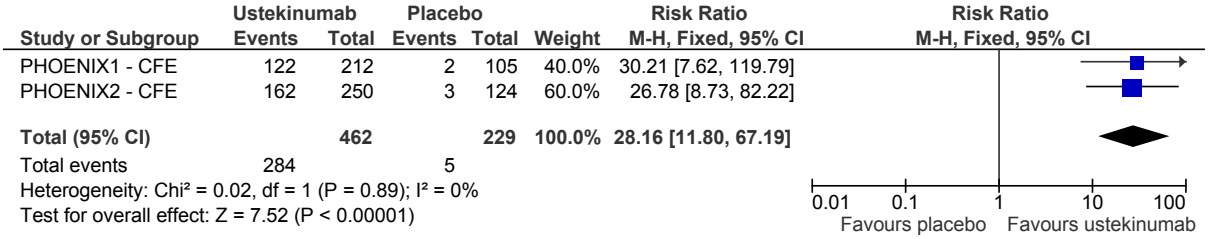


Figure 326: PASI75 (week 12)

Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PHOENIX1 - CFE	128	212	0	105	11.1%	127.90 [8.04, 2035.77]
PHOENIX2 - CFE	158	250	4	124	88.9%	19.59 [7.44, 51.61]
Total (95% CI)		**462**		**229**	**100.0%**	**31.61 [12.63, 79.11]**
Total events	286		4			

Heterogeneity: Chi² = 1.92, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 7.38 (P < 0.00001)

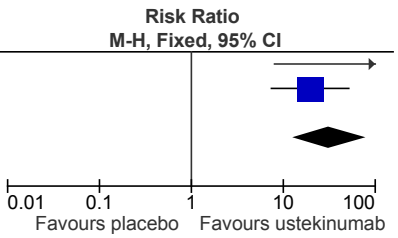


Figure 327: PASI50 (week 12)

Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PHOENIX1 - CFE	171	212	2	105	37.4%	42.35 [10.72, 167.35]
PHOENIX2 - CFE	213	250	8	124	62.6%	13.21 [6.74, 25.86]
Total (95% CI)		**462**		**229**	**100.0%**	**20.42 [6.43, 64.86]**
Total events	384		10			

Heterogeneity: Tau² = 0.44; Chi² = 2.44, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 5.12 (P < 0.00001)

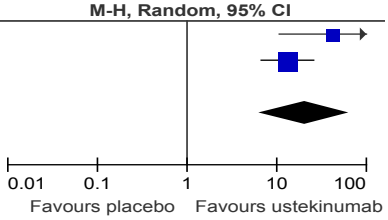


Figure 328: % improvement in PASI (week 12)

Study or Subgroup	Ustekinumab Mean	Ustekinumab SD	Ustekinumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
PHOENIX1 - CFE	73.14	27.856	208	-1.07	26.701	105	51.7%	74.21 [67.85, 80.57]
PHOENIX2 - CFE	76.61	23.638	248	-1.1	33.256	123	48.3%	77.71 [71.14, 84.28]
Total (95% CI)			**456**			**228**	**100.0%**	**75.90 [71.33, 80.47]**

Heterogeneity: Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 32.56 (P < 0.00001)

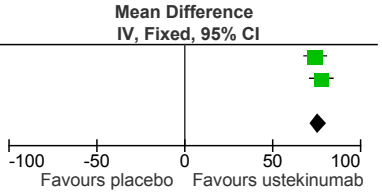


Figure 329: Change in DLQI (week 12)

Study or Subgroup	Ustekinumab Mean	Ustekinumab SD	Ustekinumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
9.6.1 Lower baseline DLQI								
PHOENIX1 - CFE	-8.9	7.15	207	0.14	5.78	105	42.0%	-9.04 [-10.51, -7.57]
Subtotal (95% CI)			**207**			**105**	**42.0%**	**-9.04 [-10.51, -7.57]**

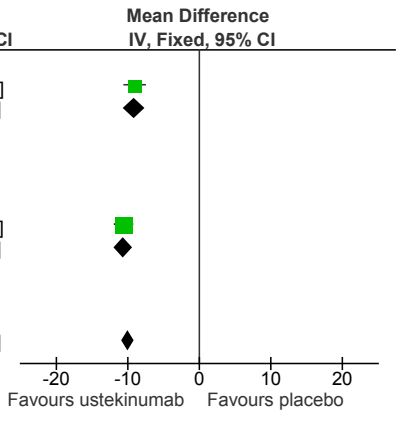
Heterogeneity: Not applicable
Test for overall effect: Z = 12.03 (P < 0.00001)

9.6.2 Higher baseline DLQI								
PHOENIX2 - CFE	-10.3	7.24	243	0.3	4.88	123	58.0%	-10.60 [-11.85, -9.35]
Subtotal (95% CI)			**243**			**123**	**58.0%**	**-10.60 [-11.85, -9.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 16.57 (P < 0.00001)

Total (95% CI)			**450**			**228**	**100.0%**	**-9.94 [-10.90, -8.99]**

Heterogeneity: Chi² = 2.50, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 20.41 (P < 0.00001)
Test for subgroup differences: Chi² = 2.50, df = 1 (P = 0.11), I² = 60.0%



J.8.5 Ustekinumab vs etanercept

Figure 330: Clear/nearly clear (PASI90; week 12)

Study or Subgroup	Ustekinumab Events	Total	Etanercept Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACCEPT - CFE	10	36	4	27	100.0%	1.88 [0.66, 5.34]
Total (95% CI)		**36**		**27**	**100.0%**	**1.88 [0.66, 5.34]**
Total events	10		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)

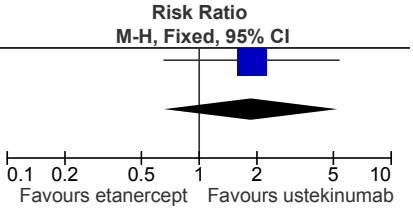


Figure 331: Clear/nearly clear (PGA; week 12)

Study or Subgroup	Ustekinumab Events	Total	Etanercept Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACCEPT - CFE	19	36	10	27	100.0%	1.43 [0.80, 2.55]
Total (95% CI)		**36**		**27**	**100.0%**	**1.43 [0.80, 2.55]**
Total events	19		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

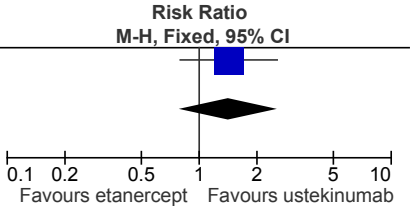


Figure 332: PASI75 (week 12)

Study or Subgroup	Ustekinumab Events	Total	Etanercept Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACCEPT - CFE	20	36	10	27	100.0%	1.50 [0.85, 2.66]
Total (95% CI)		**36**		**27**	**100.0%**	**1.50 [0.85, 2.66]**
Total events	20		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)

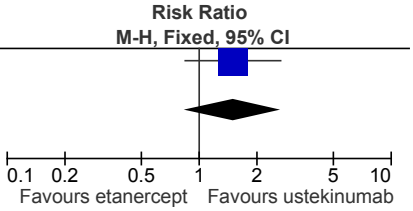


Figure 333: PASI50 (week 12)

Study or Subgroup	Ustekinumab Events	Total	Etanercept Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACCEPT - CFE	28	36	20	27	100.0%	1.05 [0.79, 1.39]
Total (95% CI)		**36**		**27**	**100.0%**	**1.05 [0.79, 1.39]**
Total events	28		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)

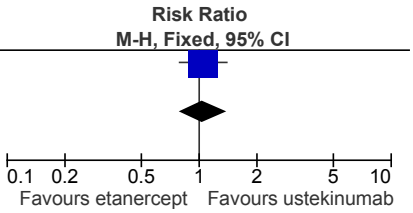
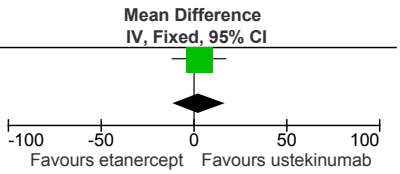


Figure 334: % improvement in PASI (week 12)

Study or Subgroup	Ustekinumab Mean	SD	Total	Etanercept Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
ACCEPT - CFE	68.3	31.676	35	65.55	25.87	27	100.0%	2.75 [-11.58, 17.08]
Total (95% CI)			**35**			**27**	**100.0%**	**2.75 [-11.58, 17.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)



J.9 Cognitive behavioural therapy

Figure 335: PASI75 at 6 months

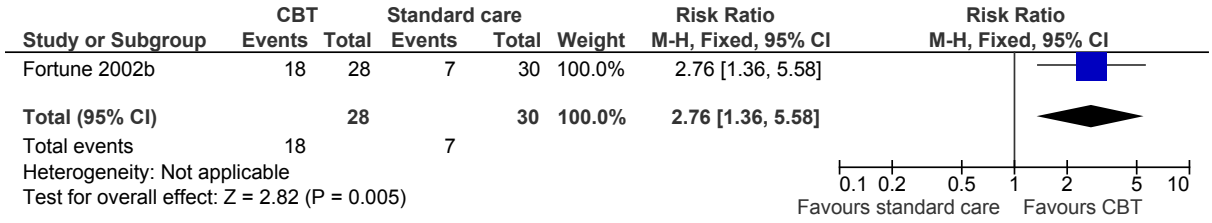
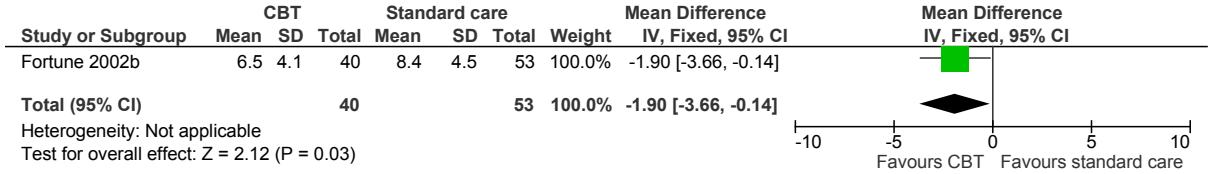


Figure 336: Final PASI at 6 weeks



J.10 Self-management

J.10.1 Additional self-management support (provided by nurse-specialist/trained practice nurse) vs standard care

Figure 337: Change in DLQI at 6 weeks-4 months

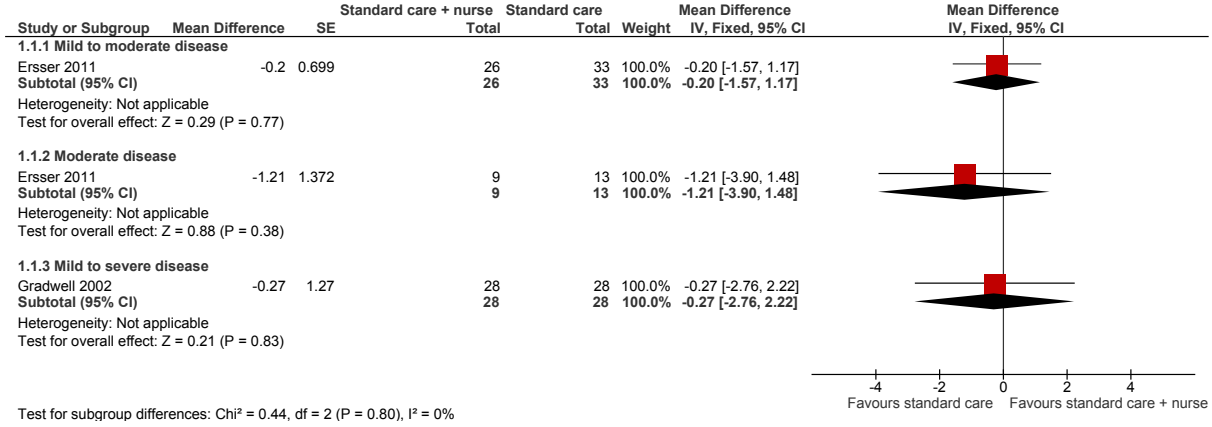


Figure 338: Change in PASI at 6 weeks

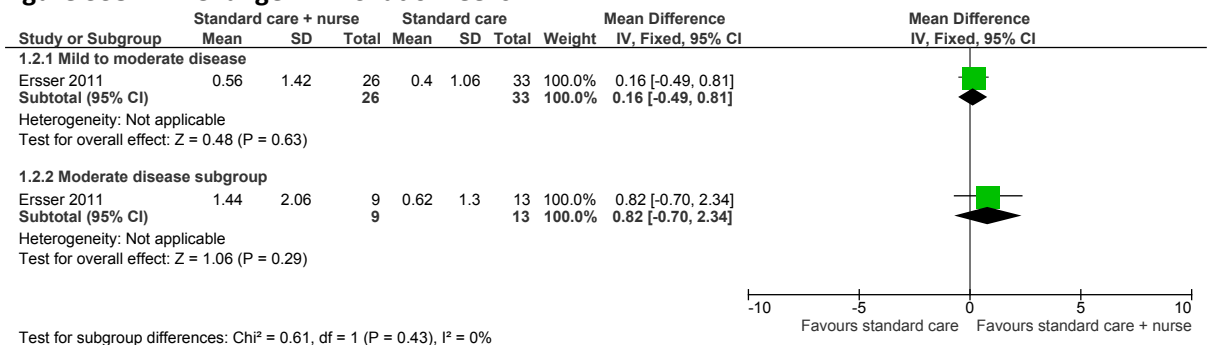


Figure 339: Treatment concordance/knowledge at 6 weeks

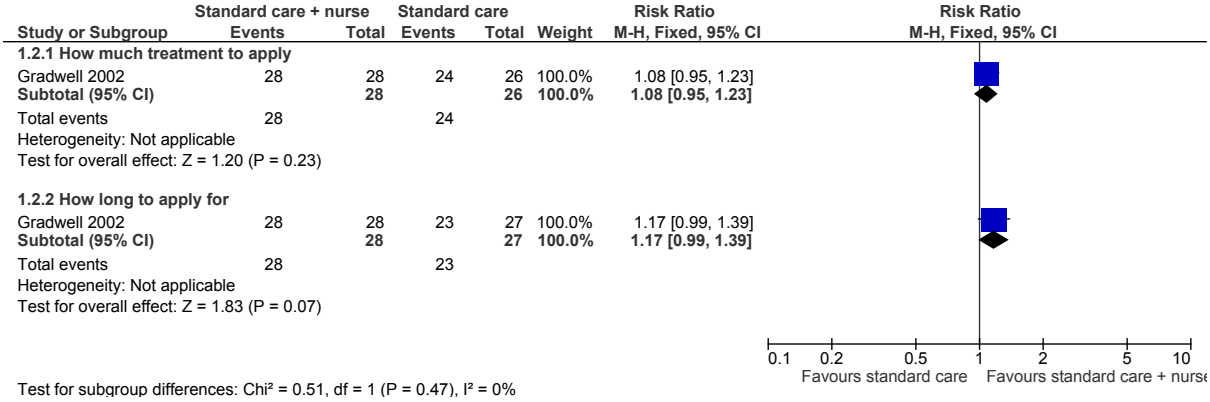
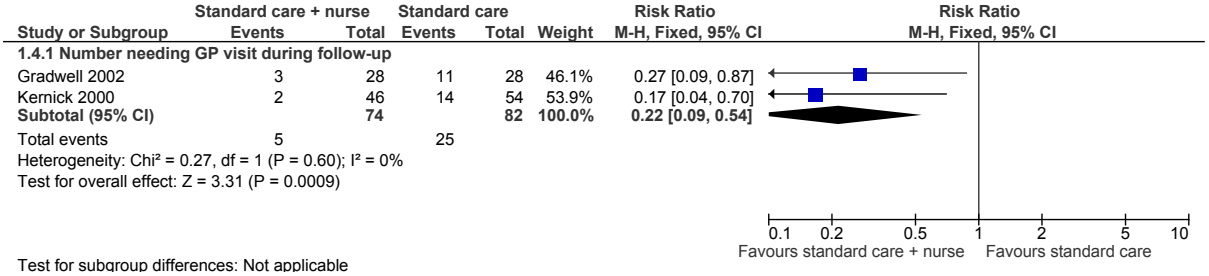
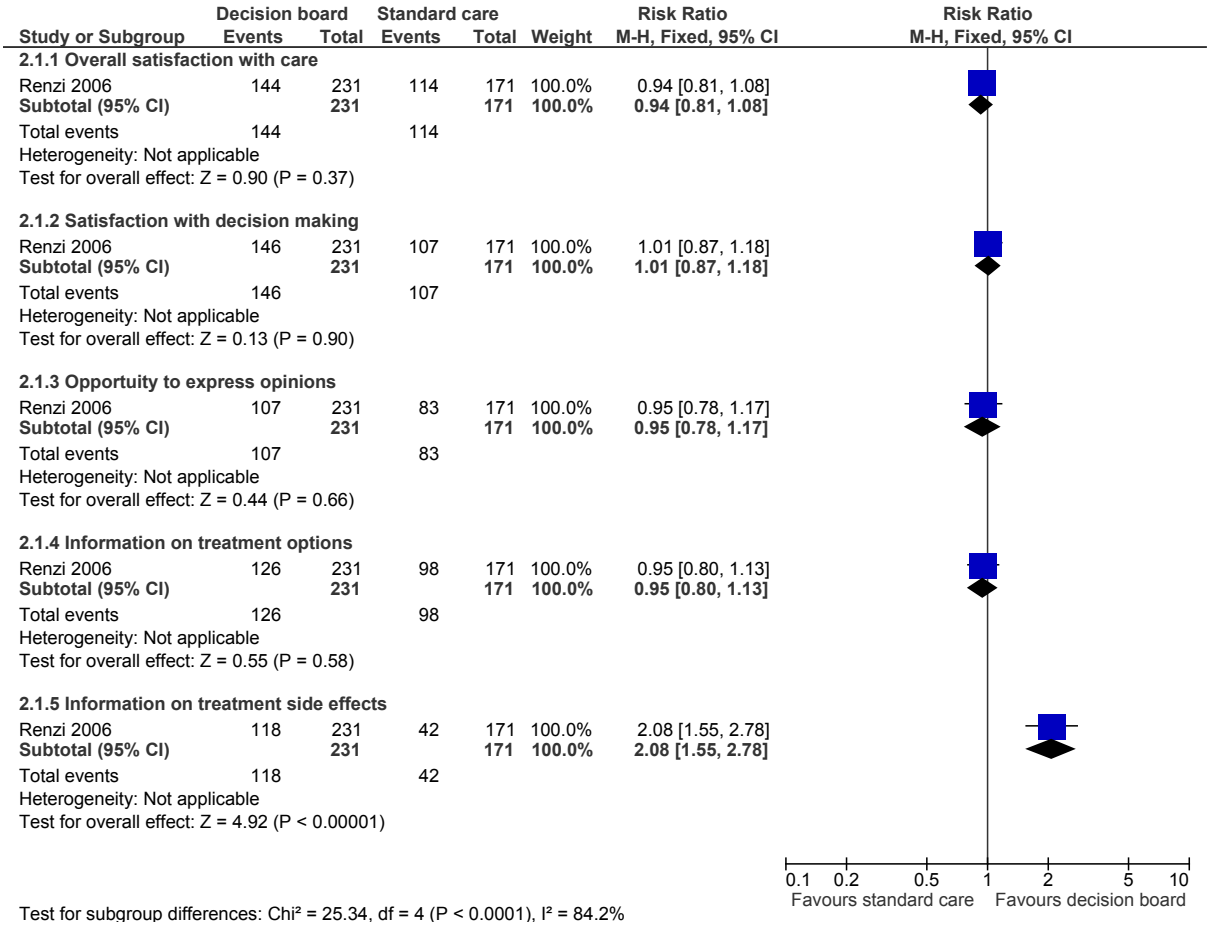


Figure 340: Additional service use required at 6-24 weeks



J.10.2 Decision board aid vs standard consultation

Figure 341: Patient satisfaction



Test for subgroup differences: Chi² = 25.34, df = 4 (P < 0.0001), I² = 84.2%

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 8) 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 8). 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 base case NMA were the same as in the clinical review (section 8.1.1), except that the one study[1] containing only children was not included. However, it was included in 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[2-16]. 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 [17] , and one study for which withdrawals were not reported by group[3].

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 8). 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 ()

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 342 and Figure 345) 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 8). 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 37 studies[3-10,14-16,18-43] from the original evidence review met the inclusion criteria for the base case in at least one network - 34 studies for the IAGI/PGA network and 14 for the PAGI network. An additional 3 studies[1,44,45]were included in the IAGI/PGA network sensitivity analysis and an additional 2 studies[1,26] 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 342 and Figure 345 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. Based on the GRADE quality ratings from the review of direct comparisons (Chapter 8 of full guideline), the evidence included in the network meta-analysis ranges in quality from very low to moderate.

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
	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			
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			

Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'			PAGI 'clear/nearly clear'		
			r	n	%	r	n	%
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			
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

Author, year	Topical	Dose	IAGI or PGA 'clear/nearly clear'			PAGI 'clear/nearly clear'		
			r	n	%	r	n	%
Camarasa, 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, 1999	Vitamin D	BD	6	89	6.7			
	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.

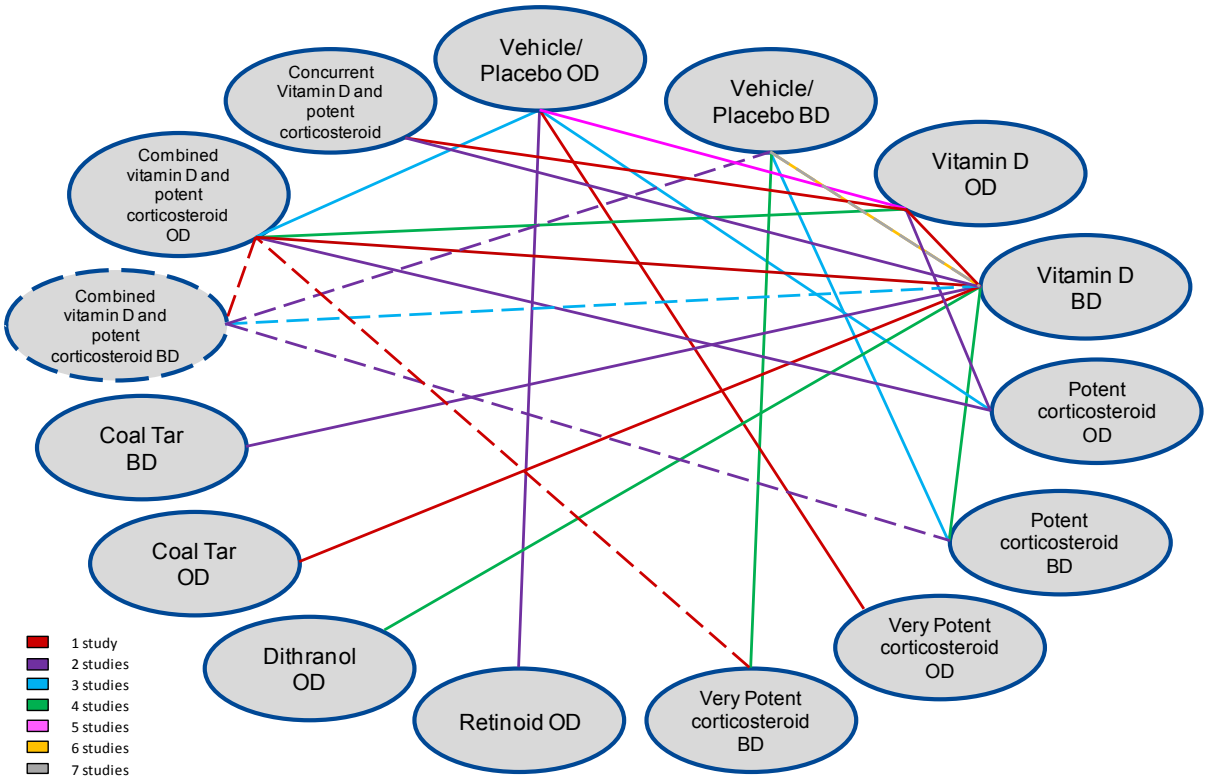
(d) The protocol for the clinical review of direct evidence included only comparisons of single topical therapies to either placebo/vehicle or vitamin D; therefore, the comparison of potent corticosteroid and coal tar was included only in the sensitivity analysis.

(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 342: Clear or nearly clear – IAGI and PGA



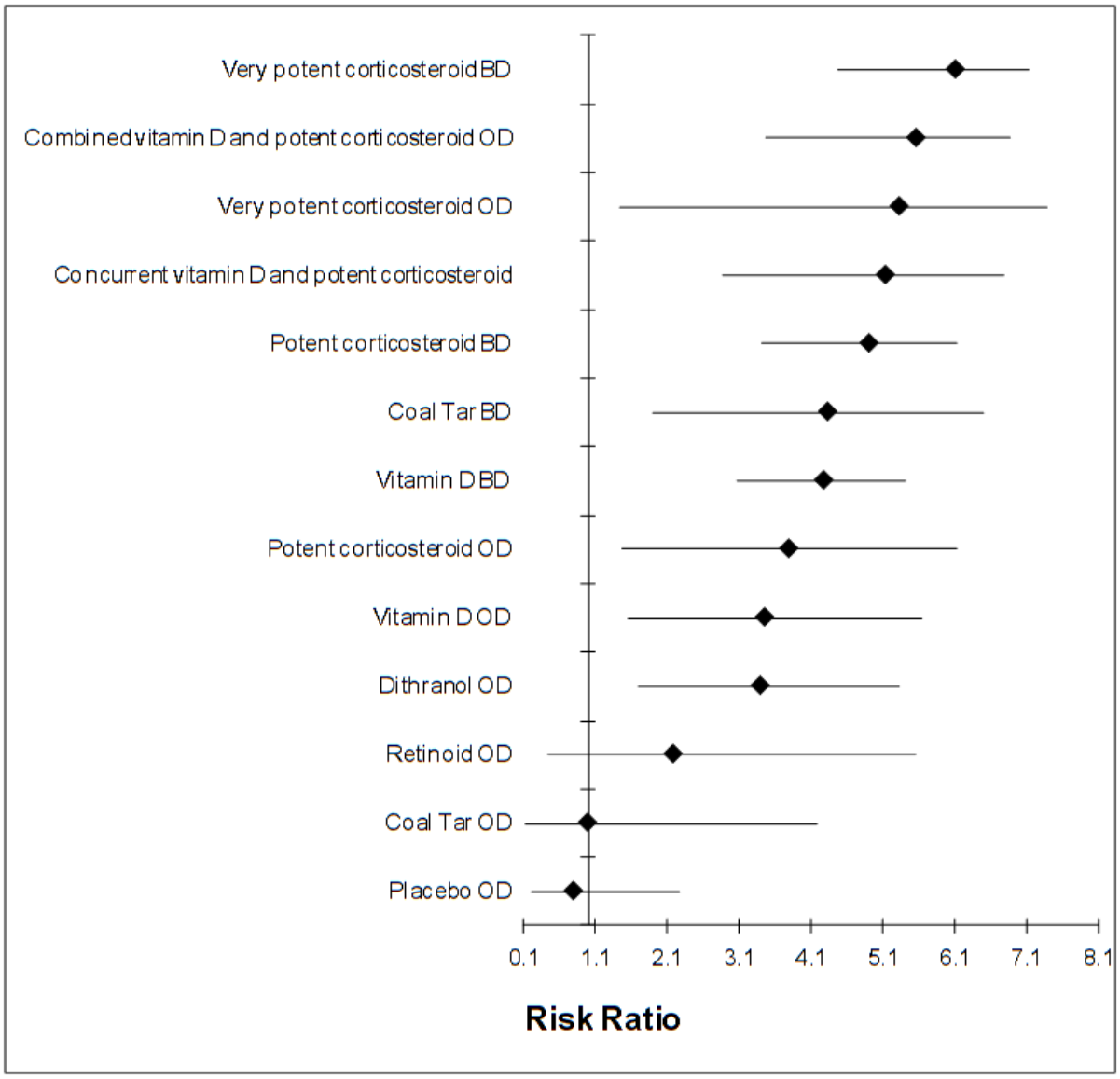
Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the base case. Dashed lines indicate all head-to-head comparisons included in the sensitivity analysis.

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 343 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	6.10	4.48	7.14	48.0%
Combined vitamin D and potent corticosteroid OD	5.55	3.49	6.88	12.7%
Very potent corticosteroid OD	5.31	1.44	7.38	25.3%
Concurrent vitamin D and potent corticosteroid	5.12	2.87	6.78	7.9%
Potent corticosteroid BD	4.90	3.40	6.14	2.1%
Coal Tar BD	4.32	1.90	6.49	3.6%
Vitamin D or vitamin D analogue BD	4.26	3.06	5.42	0.0%
Potent corticosteroid OD	3.78	1.46	6.14	0.2%
Vitamin D or vitamin D analogue OD	3.44	1.56	5.63	0.0%
Dithranol OD	3.38	1.71	5.34	0.1%
Tazarotene OD	2.17	0.43	5.57	0.2%
Coal Tar OD	0.98	0.12	4.18	0.0%
Placebo OD	0.78	0.21	2.29	0.0%

Figure 343: 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 343. 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 344, indicate that there are very few comparisons for which the treatment effect reaches statistical significance.

A few exceptions include:

- 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 analogue 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 344: 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**				
1.324 0.354 to 5.435	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***				
7.175 **3.268 to 17.95**	**5.395** **1.702 to 18.1**	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**			
10.92 **3.214 to 41**	**8.273** **4.406 to 15.7**	1.53 0.513 to 4.361	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**
8.537 **3.373 to 23.34**	**6.429** **1.564 to 26**	1.19 0.445 to 2.969	0.7805 0.199 to 2.929	Potent corticosteroid OD					**2.15** **1.69 to 2.73**				
15.39 **3.885 to 67.64**	**11.61** **5.286 to 25.9**	2.15 0.6 to 7.331	1.405 0.706 to 2.779	1.807 0.42 to 8.074	Potent corticosteroid BD							***0.10*** ***0.03 to 0.34***	
19.58 **3.332 to 119.5**	**14.78** **1.536 to 138**	2.723 0.355 to 18.65	1.784 0.195 to 15.8	2.295 0.3 to 17.24	1.27 0.126 to 12.38	Very potent corticosteroid OD							
33.62 **6.378 to 216.1**	**25.03** **9.276 to 81.1**	4.657 0.979 to 23.86	3.028 0.936 to 11.31	3.908 0.72 to 25.03	2.172 0.607 to 8.889	1.706 0.153 to 22.65	Very potent corticosteroid BD		0.71 0.29 to 1.71				
3.468 0.976 to 13.29	2.623 0.4 to 17.3	0.4855 0.101 to 2.264	0.3183 0.052 to 1.959	0.4085 0.08 to 2.084	0.2247 0.033 to 1.576	0.1772 0.02 to 1.646	**0.104** **0.01 to 0.881**	Retinoid OD					
22.62 **9.679 to 59.38**	**17.09** **5.524 to 53.7**	**3.17** **1.527 to 6.252**	2.06 0.713 to 5.906	**2.658** **1.04 to 6.969**	1.471 0.427 to 5.083	1.161 0.16 to 8.943	0.6785 0.14 to 3.084	**6.514** **1.336 to 31.57**	Combined vitamin D and Potent corticosteroid OD				
17.47 **4.275 to 82.75**	**13.2** **3.965 to 47.8**	2.441 0.675 to 8.88	1.595 0.554 to 4.973	2.06 0.46 to 9.925	1.131 0.327 to 4.256	0.904 0.09 to 9.437	0.5236 0.1 to 2.652	5.035 0.721 to 36.72	0.7733 0.209 to 3.009	Concurrent vitamin D and Potent corticosteroid			
1.286 0.108 to 14.48	0.9741 0.105 to 7.9	0.1786 0.016 to 1.702	**0.117** **0.014 to 0.868**	0.15 0.01 to 1.693	**0.083** **0.009 to 0.694**	0.06566 0.003 to 1.337	**0.038** **0 to 0.385**	0.369 0.021 to 5.508	**0.057** **0.005 to 0.549**	**0.073** **0.006 to 0.706**	Coal Tar OD		
11.27 **2.021 to 73.21**	**8.513** **2.196 to 35.1**	1.574 0.313 to 8.21	1.029 0.31 to 3.614	1.311 0.22 to 8.556	0.7334 0.186 to 3.054	0.5774 0.048 to 7.836	0.3378 0.06 to 1.86	3.224 0.37 to 30.55	0.4959 0.101 to 2.633	0.6423 0.124 to 3.362	8.827 0.86 to 107.7	Coal Tar BD	
6.888 **1.61 to 34.2**	**5.23** **1.904 to 15**	0.9658 0.248 to 3.719	0.6312 0.283 to 1.449	0.8107 0.17 to 4.083	0.4484 0.158 to 1.334	0.3554 0.035 to 3.933	**0.2089** **0.04 to 0.875**	1.987 0.272 to 14.8	0.3063 0.081 to 1.193	0.3947 0.1 to 1.545	5.409 0.625 to 54.82	0.6158 0.137 to 2.648	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 (48%), twice daily very potent corticosteroid emerges as the most effective topical. In a further 25% of simulations, once daily very potent corticosteroid emerged as the most effective topical. This means that in nearly three quarters 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, rarely ranking better than 3rd least effective among the 40,000 simulations.

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.

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.

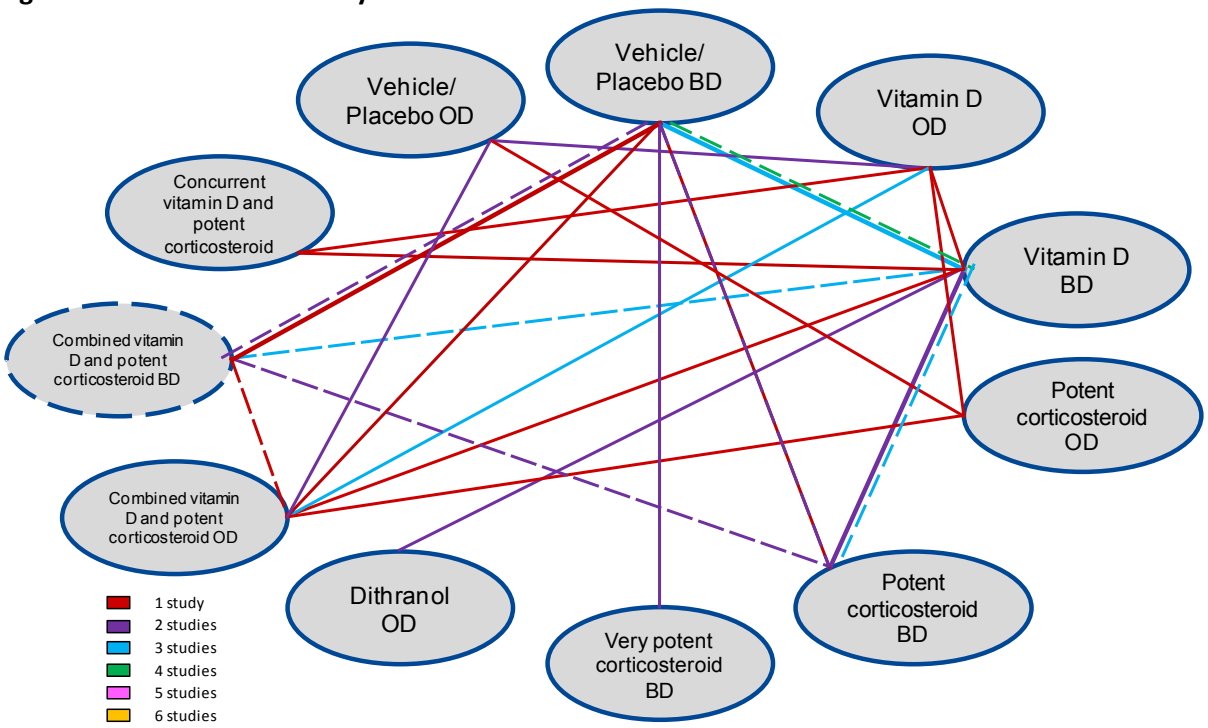
As indicated by the high relative risks for twice daily very potent corticosteroid and combined or concurrent vitamin D or vitamin D analogues and potent corticosteroid, these were consistently ranked among the most effective (i.e. most to 3rd most effective).

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 22.6 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 Guenther 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.4.6 Clear/nearly clear as measured by PAGI

Figure 345 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 345: Clear or nearly clear - PAGI



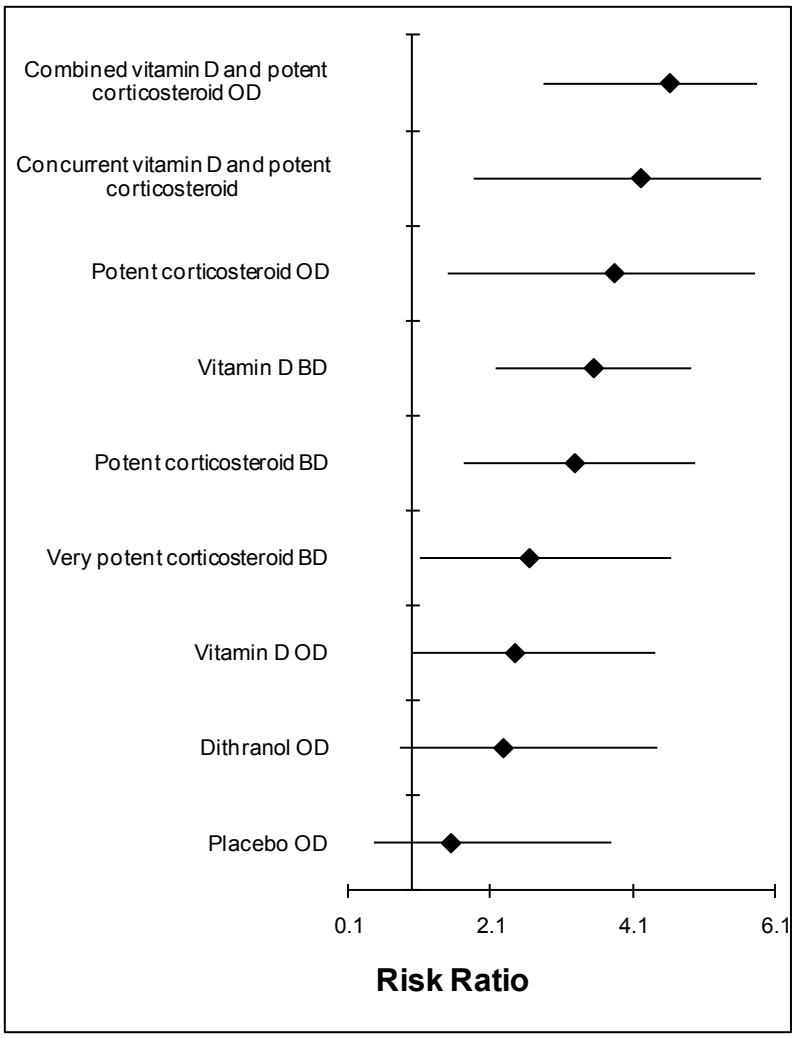
Note: Solid lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the base case. Dashed lines indicate all head-to-head comparisons included in the sensitivity analysis.

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 346 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 346: 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 346. 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 347: 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 the most effective treatment 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:

- Two studies which were excluded from the review of direct evidence on the basis that they did not report an included *comparison* (even though each treatment being compared was included somewhere in the review). Hence these added greater statistical power to the analysis.
    - One study(Thawornchaisit, 2007) compared twice daily potent corticosteroid with twice daily crude coal tar.

  - Another study (Menter, 2009) compared once daily combined product containing vitamin D analogue and potent corticosteroid with twice daily very potent corticosteroid.
- A study conducted entirely in children(Oranje, 1997).
- A further comparator– 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.
- Data from one study (Papp, 2003) for the PAGI outcome (it was excluded from the clinical review of direct evidence given that in the paper it was reported graphically).

The dashed lines in Figure 342 and Figure 345 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 – Sensitvity analysis wherein all data and twice daily combined vitamin D analogue and potent corticosteroid are included

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	5.915	4.820	6.567	45.6	NA
Very potent corticosteroid BD	5.736	4.468	6.549	29.0	48.0
Combined vitamin D and potent corticosteroid OD	5.206	3.667	6.249	3.2	12.7
Very potent corticosteroid OD	4.961	1.526	6.816	18.7	25.3
Potent corticosteroid BD	4.716	3.464	5.736	0.3	2.1
Concurrent vitamin D and potent corticosteroid	4.691	2.677	6.169	2.9	7.9
Vitamin D or vitamin D analogue BD	3.845	2.845	4.789	0.0	0.0
Potent corticosteroid OD	3.560	1.584	5.537	0.1	0.2
Vitamin D or vitamin D analogue OD	3.213	1.655	4.988	0.0	0.0
Dithranol OD	3.018	1.551	4.751	0.0	0.1
Coal Tar BD	2.921	1.303	4.895	0.0	3.6
Tazarotene OD	2.008	0.459	4.936	0.1	0.2
Coal Tar OD	0.852	0.103	3.617	0.0	0.0
Placebo OD	0.729	0.229	1.910	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 348) indicate that based on direct evidence from one study (Guenther, 2002) 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 1.77 (0.62 to 5.03)).

Figure 348: 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**					
1.431 0.446 to 4.902	Placebo BD		**7.73** **5.81 to 10.29**		**12.47** **6.81 to 22.85**		**14.67** **8.84 to 24.34**		**17** **9.55 to 30.27**	**31.47** **20.09 to 49.3**				
7.142 **3.337 to 17.18**	**5.002** **1.851 to 14**	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**			
10.19 **3.285 to 33.61**	**7.116** **4.054 to 12.4**	1.429 0.527 to 3.56	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**
8.694 **3.506 to 22.67**	**6.074** **1.75 to 20.8**	1.215 0.474 to 2.897	0.8544 0.255 to 2.801	Potent corticosteroid OD					**2.15** **1.69 to 2.73**					
16.85 **4.94 to 63.87**	**11.8** **5.756 to 24.5**	2.362 0.773 to 7.017	1.66 0.908 to 3.141	1.937 0.53 to 7.439	Potent corticosteroid BD					**2.48** **1.97 to 3.11**			**0.10** **0.03 to 0.34**	
19.58 **3.577 to 117.6**	**13.78** **1.667 to 113**	2.75 0.397 to 18.78	1.931 0.24 to 15.58	2.282 0.31 to 16.33	1.164 0.133 to 10.04	Very potent corticosteroid OD								
35.15 **9.602 to 146.4**	**24.45** **10.17 to 63.4**	**4.91** **1.505 to 16.51**	**3.447** **1.3 to 9.998**	**4.038** **1.07 to 16.81**	2.078 0.691 to 6.521	1.785 0.203 to 16.92	Very potent corticosteroid BD		0.71 0.29 to 1.71					
3.408 **1.012 to 12.54**	2.398 0.422 to 13.6	0.4789 0.106 to 2.114	0.3363 0.061 to 1.877	0.394 0.08 to 1.937	0.203 0.033 to 1.212	0.1751 0.02 to 1.486	**0.09726** **0.01 to 0.607**	Retinoid OD						
23.24 **10.1 to 58.29**	**16.26** **6.445 to 41.2**	**3.262** **1.632 to 6.308**	2.285 0.94 to 5.677	**2.676** **1.1 to 6.809**	1.377 0.479 to 3.874	1.186 0.169 to 8.285	0.6661 0.21 to 1.916	**6.815** **1.461 to 31.4**	Combined vitamin D and Potent corticosteroid OD	**1.61** **1.03 to 2.5**				
41.25 **11.95 to 154.8**	**28.76** **12.6 to 65.4**	**5.766** **1.808 to 17.43**	**4.04** **1.924 to 8.588**	**4.722** **1.27 to 18.45**	**2.439** **1.056 to 5.512**	2.11 0.241 to 18.54	1.174 0.35 to 3.64	**11.99** **2.003 to 72.13**	1.765 0.616 to 5.031	Combined vitamin D and Potent corticosteroid BD				
16.56 **4.394 to 70.52**	**11.63** **3.672 to 37.5**	2.325 0.699 to 7.593	1.635 0.576 to 4.766	1.906 0.47 to 8.315	0.986 0.291 to 3.311	0.8446 0.092 to 7.959	0.4749 0.11 to 1.866	4.843 0.742 to 32.97	0.7147 0.212 to 2.472	0.4043 0.116 to 1.458	Concurrent vitamin D and Potent			
1.201 0.104 to 11.78	0.8321 0.09 to 6.27	0.1677 0.015 to 1.458	**0.1172** **0.013 to 0.818**	0.137 0.01 to 1.391	**0.07019** **0.007 to 0.542**	0.06025 0.003 to 1.067	**0.03387** **0 to 0.295**	0.3478 0.022 to 4.625	**0.05099** **0.005 to 0.448**	**0.02874** **0.003 to 0.238**	**0.07127** **0.006 to 0.652**	Coal Tar OD		
6.038 **1.349 to 28.88**	**4.235** **1.37 to 13.2**	0.8463 0.208 to 3.274	0.595 0.218 to 1.645	0.6932 0.15 to 3.351	0.3574 0.121 to 1.044	0.3078 0.031 to 3.183	**0.1721** **0.04 to 0.68**	1.757 0.244 to 12.78	**0.2596** **0.069 to 0.992**	**0.1469** **0.043 to 0.504**	0.3618 0.083 to 1.56	5.12 0.563 to 55.45	Coal Tar BD	
6.392 **1.625 to 26.99**	**4.479** **1.703 to 12.1**	0.9 0.254 to 3.005	0.6304 0.286 to 1.407	0.7394 0.18 to 3.175	0.3793 0.137 to 1.039	0.3253 0.036 to 3.083	**0.1829** **0.05 to 0.64**	1.87 0.286 to 12.57	**0.2754** **0.083 to 0.906**	**0.1559** **0.052 to 0.467**	0.3856 0.102 to 1.42	5.395 0.671 to 53.85	1.061 0.294 to 3.816	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 - sensitivity analysis wherein all data and twice daily combined vitamin D analogue and potent corticosteroid are included

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 349) 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 349: 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 37 studies, including up to 13,887 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. . The estimates and ranking of strategies were largely consistent with the base case analysis; 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 (Base case analysis)

```
#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=34,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
 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(-3,-1,3,-1,0,3,-2,-2,-1,-3,0,-1,2,3,3,2,3,3,1,3,-2,-2,3,-2,3,3,3,1,-1,1,1,-1,1,-1),

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,-3,NA,-3,NA,NA,NA,NA,-2,NA,NA,NA,NA,NA,NA,-
1,NA,2,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,NA,1,NA,NA,NA,NA,NA,NA,-
2,NA,NA,NA,NA,NA,NA,NA,NA,1,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
2,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,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,1,NA,NA,NA,NA,NA,
NA,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA
,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
1,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
2,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,NA,-

3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
3,NA,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
,NA,0,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,NA,-
2,NA,NA,NA,NA,NA,NA,NA,NA,NA,2,NA,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,
NA,-1,NA,NA,NA,NA,NA,NA,NA,NA,NA,-2,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,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,NA,NA,NA,2,NA,NA,NA,NA,NA,NA,NA,NA,N
A,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,2,NA,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,NA,0,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,0

),.Dim=c(34 , 14))))

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 8) 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 and potent corticosteroid)
- There are frequently multiple overlapping comparisons (for example vitamin D vs potent corticosteroid, vitamin D vs combined vitamin D and potent corticosteroid and potent corticosteroid vs combined vitamin D 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 8). 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 8).

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[46-55].

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 8). 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 and twice daily vitamin D 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 OD
- Vitamin D BD
- Potent corticosteroid OD
- Potent corticosteroid BD
- Very potent corticosteroid OD
- Very potent corticosteroid BD
- Combined vitamin D 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 (Figure 3427) 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 8). 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[46-59] from the original evidence review met the inclusion criteria for the network. Table 1 presents all the available data used in the analysis for investigator assessed outcomes. Figure 342 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. Based on the GRADE quality ratings from the review of direct comparisons (Chapter 8 of full guideline), the evidence included in the network meta-analysis ranges in quality from very low to moderate.

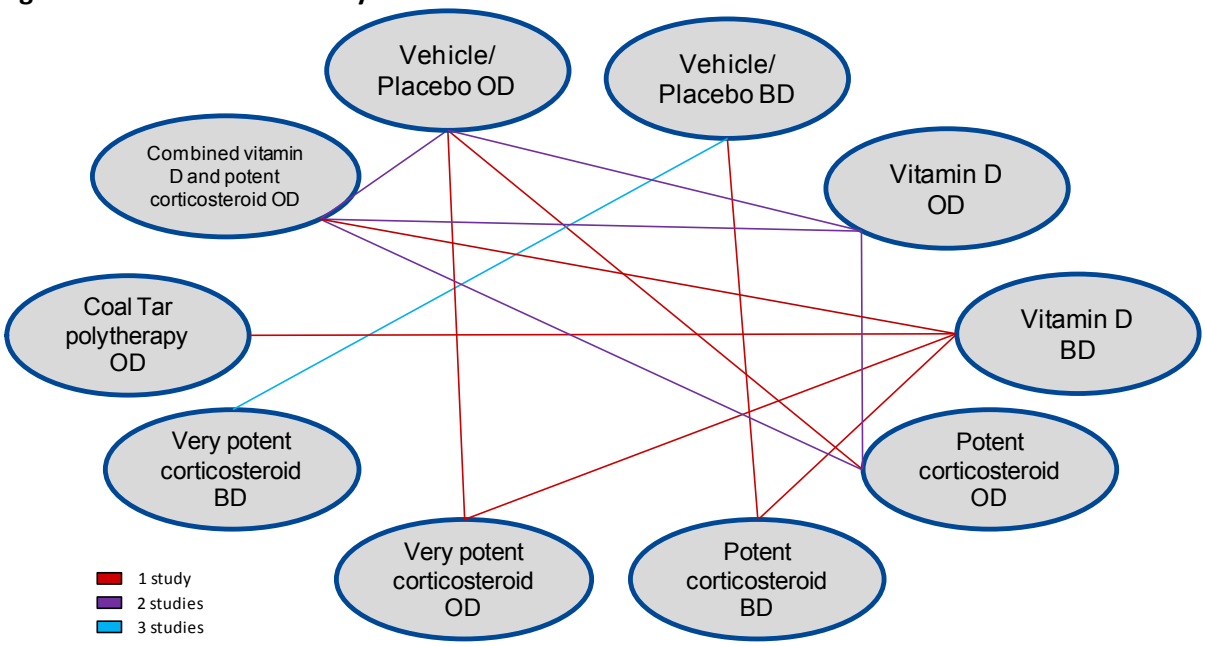
Table 6: Study characteristics and IAGI/PGA and PAGI efficacy data used in networks

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	OD	15	25	60.0%
Jarratt 2004	Placebo	OD	1	47	2.1%
	Very potent corticosteroid	OD	40	95	42.1%
Jemec 2008	Placebo	OD	31	136	22.8%
	Vitamin D	OD	100	272	36.8%
	Potent corticosteroid	OD	356	556	64.0%
	Combined vitamin D and potent corticosteroid	OD	385	541	71.2%
Klaber 1994	Vitamin D	BD	138	236	58.5%
	Potent corticosteroid	BD	175	232	75.4%
Kragballe 2009	Vitamin D	BD	33	105	31.4%
	Combined vitamin D and potent corticosteroid	OD	142	207	68.6%
McKinnon 2000	Vitamin D	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	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 and potent corticosteroid	OD	97	135	71.9%
van de Kerkhof 2009	Vitamin D	OD	124	286	43.4%
	Potent corticosteroid	OD	343	562	61.0%
	Combined vitamin D 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 and potent corticosteroid to very potent corticosteroid.

Figure 350: Clear or nearly clear – IAGI and PGA



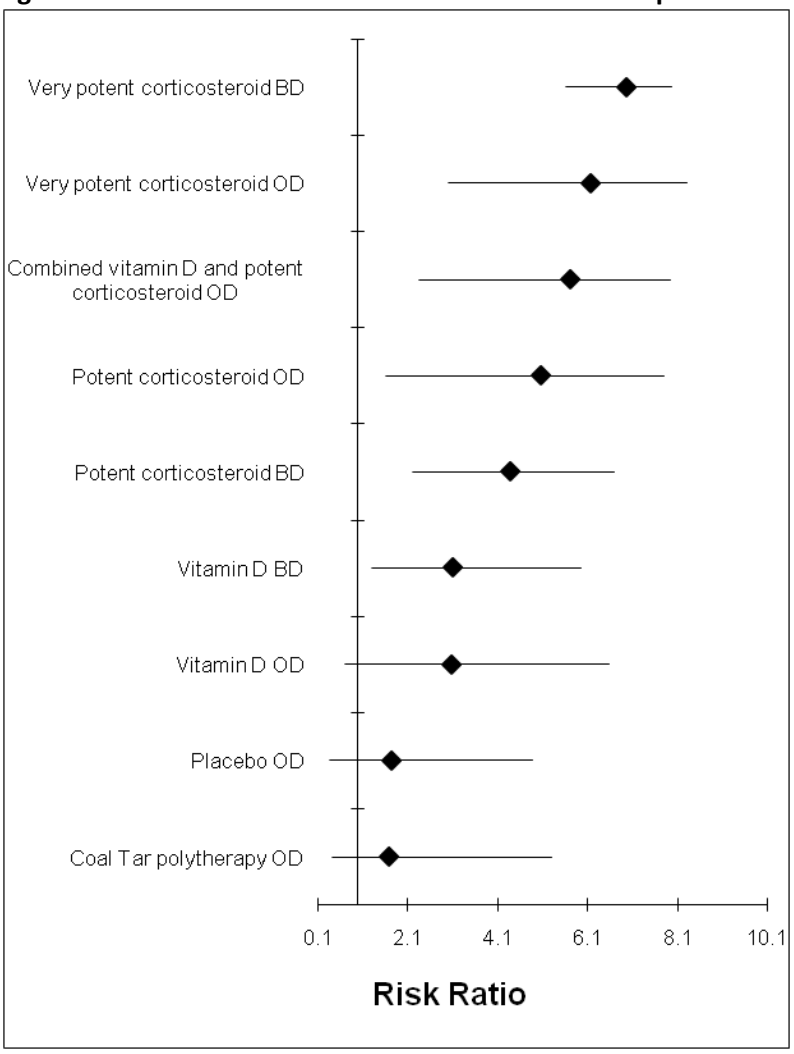
Note: Lines indicate direct head-to-head comparisons and the colour indicates the number of trials per comparison included in the analysis.

Table 2 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 343 presents these estimates and their uncertainty as a forest plot.

Table 7: 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	6.958	5.615	7.960	66.0%
Very potent corticosteroid OD	6.151	2.992	8.306	22.8%
Combined vitamin D and potent corticosteroid OD	5.705	2.349	7.951	7.7%
Potent corticosteroid OD	5.039	1.610	7.793	2.0%
Potent corticosteroid BD	4.379	2.217	6.680	0.4%
Vitamin D BD	3.099	1.308	5.942	0.0%
Vitamin D OD	3.072	0.713	6.587	0.0%
Placebo OD	1.736	0.367	4.890	0.0%
Coal Tar polytherapy OD	1.680	0.417	5.290	0.1%

Figure 351: 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 and once daily vitamin D analogue 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 Table 2 and Figure 343. 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 Figure 344, 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 daily vitamin D
- Once and twice daily very potent corticosteroids are more effective than once and twice daily vitamin D and once daily coal tar polytherapy

Once daily combined vitamin D and potent corticosteroid is more effective than once daily vitamin D and once daily coal tar polytherapy.

Figure 352: 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**	
0.522 0.104 to 2.946	Placebo BD				**5.43** **2.60 to 11.34**		**25.78** **16.00 to 41.53**		
2.163 0.864 to 5.69	4.168 0.688 to 22.6	Vitamin D OD		**2.50** **2.00 to 3.03**				**3.43** **2.78 to 4.24**	
2.169 **0.78 to 9.177**	**4.224** **1.361 to 15.9**	1.001 0.332 to 4.505	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**
5.401 **2.16 to 14.18**	**10.34** **1.745 to 56.5**	**2.499** **1.106 to 5.521**	2.492 0.553 to 7.495	Potent corticosteroid OD				**1.39** **1.16 to 1.65**	
3.98 0.925 to 20.91	**7.665** **2.622 to 23.9**	1.849 0.398 to 10.43	1.838 0.592 to 4.573	0.7373 0.16 to 4.144	Potent corticosteroid BD				
9.115 **3.09 to 47.85**	**17.76** **4.003 to 114**	**4.203** **1.256 to 25.22**	**4.176** **1.509 to 14.06**	1.679 0.5 to 10.1	2.297 0.603 to 12.95	Very potent corticosteroid OD			
14.7 **2.586 to 107.8**	**28.52** **13.55 to 68.1**	**6.825** **1.112 to 51.16**	**6.762** **1.485 to 27.91**	2.729 0.45 to 20.76	3.716 0.975 to 14.86	1.607 0.221 to 9.039	Very potent corticosteroid BD		
7.393 **3.421 to 16.44**	**14.16** **2.835 to 67.3**	**3.411** **1.579 to 7.591**	3.393 0.957 to 8.485	1.364 0.64 to 2.964	1.852 0.396 to 7.346	0.8078 0.162 to 2.404	0.4997 0.076 to 2.709	Combined vitamin D and Potent corticosteroid OD	
0.9511 0.219 to 6.492	1.839 0.388 to 11.6	0.4389 0.094 to 3.185	0.4374 0.136 to 1.42	0.1755 0.04 to 1.26	0.2371 0.056 to 1.288	**0.1051** **0.019 to 0.4782**	**0.06447** **0.011 to 0.459**	**0.1288** **0.032 to 0.775**	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 8, 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 and once daily vitamin D analogue, 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 very potent corticosteroid. The topical with the third best expected efficacy was once daily two-compound formulation product (potent corticosteroid and vitamin D analogue). In general, products containing potent or very potent corticosteroids were more effective than products without corticosteroids; however, this trend did not reach significance in all cases. Once daily potent corticosteroid and once daily two-compound formulation product were both significantly better than once daily vitamin D analogue and very potent corticosteroids (once and twice daily) were significantly better than once and twice daily vitamin D analogues. Vitamin D analogues, although more effective than placebo, were among the least effective overall, only a bit better than coal tar polytherapy.

No consistent trend linking frequency of application to improved efficacy was observed. Once and twice daily vitamin D analogues were roughly equal in effect (OR=1.001, 95% CrI: 0.33 to 4.51), whereas once daily potent corticosteroids may be better than twice daily (OR=0.74, 95% CrI: 0.16 to 4.14) and twice daily very potent corticosteroids may be better than once daily (OR=1.607, 95% CrI: 0.22 to 9.04). This was inconsistent with the results of the NMA for the treatment of trunks and limbs in which twice daily was found to be more effective in general than once daily. 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 7 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,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))))
```

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

M.1 Introduction

The review of clinical evidence for topical therapies used in the treatment of individuals with mild to moderate plaque psoriasis showed that there were a wide variety of options – emollients, tars, dithranol, retinoids, corticosteroids (potent and very potent), vitamin D analogues and combination products – each associated with certain advantages and disadvantages. The results of the network meta-analysis indicated that some interventions, such as combined or concurrent vitamin D analogue and potent corticosteroid, were more likely to induce clearance or near clearance than others. Given that these combined and concurrent application strategies carry additional cost compared to both their individual constituent parts and compared to other topical alternatives, it is important to consider whether these additional costs are justified by additional health benefits in terms of improved quality of life.

Three cost-effectiveness analyses were identified in the published literature, but each had methodological limitations that called its conclusions into question. The analysis by Ashcroft and colleagues[60] was based on only one trial and included only two of the interventions of interest (dithranol and calcipotriol). The analysis by Oh and colleagues[61] was quite old and had a fairly confusing model structure. The analysis by Bottomley and colleagues,[62] although the most applicable of the included studies, used an unadjusted indirect comparison to inform the treatment effect estimates, which likely overestimated the effectiveness of some interventions and underestimated the effectiveness of others. Bottomley and colleagues also did not include all the possible comparators of interest.

Due to the limitations of the available economic evidence and the importance of this area in clinical practice, the GDG considered the development of an original cost-effectiveness model to evaluate topical therapies to be a high priority. The decision modelling presented here was developed in close collaboration between the health economist, NCGC technical team and GDG members.

M.2 Methods

M.2.1 Model overview

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

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

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

The performance of alternative treatment sequences was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness.

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

M.2.1.1 Comparators

The aim of the analysis was to identify the most cost-effective sequence of first, second and third line topical therapies. It was important to model sequences given that most patients will commence treatment with one topical and then try others before moving on to more intensive treatments such as phototherapy and/or systemic therapy. Table 8 presents the list of possible first, second and third line treatments which may be combined in a sequence.

Table 8: All possible sequences of first, second and third line interventions

First line	Second line	Third line
Vitamin D OD	Vitamin D OD	Vitamin D OD
Vitamin D BD	Vitamin D BD	Vitamin D BD
Potent corticosteroid OD	Potent corticosteroid OD	Potent corticosteroid OD
Potent corticosteroid BD	Potent corticosteroid BD	Potent corticosteroid BD
Two-compound formulation product (TCF) OD	TCF OD	TCF OD
Concurrent am/pm	Concurrent am/pm	Concurrent am/pm
		Dithranol OD
		Coal tar BD
		Referral

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

- Concurrent treatment with vitamin D analogue and potent corticosteroid would not come after a failure of once daily two-compound formulation product;
- Once daily treatment with a given topical would not come after a failure of twice daily treatment with the same topical;
- Once daily treatment with potent steroid or vitamin D analogue would not come after concurrent treatment with vitamin D analogue and potent corticosteroid or once daily two-compound formulation product;
- No strategy could include potent corticosteroids among all three lines of treatment (including as part of concurrent vitamin D analogues and potent corticosteroid or TCF product).

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

Due to the unacceptability of dithranol and coal tar as routine treatments (difficult application, risk of staining, strong and unpleasant odours, etc), these treatments were reserved for third line treatment only. This reflects their current placement in primary care given the availability of more acceptable and effective topicals such as those being compared as first and second line topicals.

M.2.1.2 Population

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

M.2.1.3 Time horizon, perspective, discount rates used

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

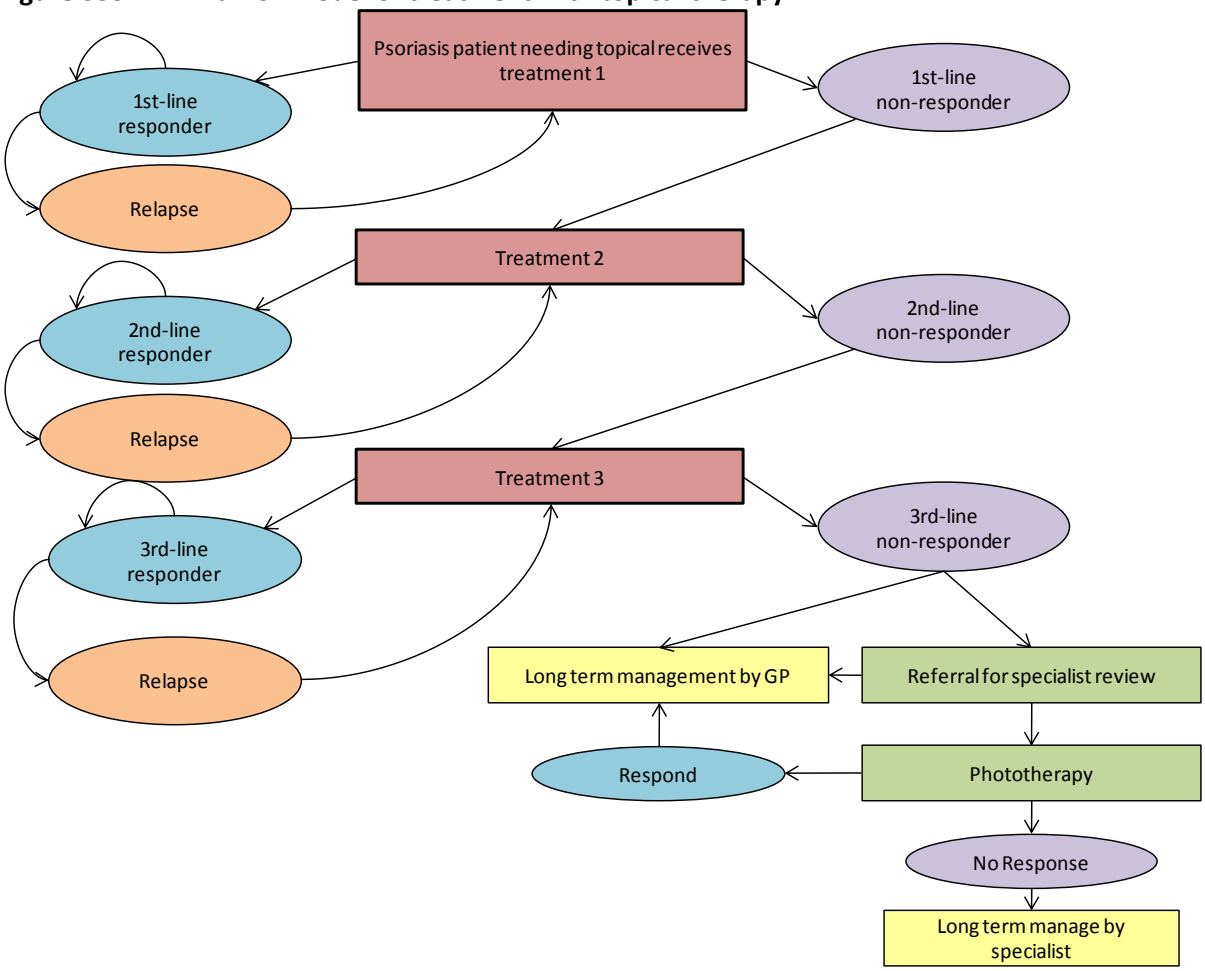
M.2.2 Approach to modelling

M.2.2.1 Model structure

A Markov model was constructed in TreeAge Pro 2009 to capture the different costs and effects associated with a given sequence of topical treatments. It was built to reflect transitions between a set of mutually exclusive health states, defined by response and non-response to treatment. The Markov model and how patients move through the pathway is illustrated in Figure 353. The structure of the model developed by the NCGC was adapted from the model developed by Bottomley and colleagues[62] and was validated by the GDG as a reasonable reflection of current clinical practice.

The consequences of a given topical treatment are reflected as a set of possible transitions between health states over a series of discrete time periods, called cycles. In Figure 353, health states are depicted as ovals and interventions are depicted as rectangles. Movement between various health states is governed by transition probabilities, derived from the systematic review of clinical effectiveness data. Thirteen 4-week cycles were modelled, resulting in a 1-year time horizon for the analysis, with a half-cycle correction applied.

Figure 353: Markov model of treatment with topical therapy



The model assumes that all hypothetical patients commence treatment with a given topical and experience one of two outcomes: response (defined as clearance/near clearance of their psoriasis) or no response (defined as something less than clearance/near clearance of their psoriasis). Patients who achieve clearance/near clearance are assumed to stop treatment and either maintain clearance/near clearance in the absence of treatment or they relapse. Patients who relapse are assumed to resume treatment with the same topical and again face a probability of responding or not responding. Patients who fail to achieve clearance on a given topical are assumed to return to their GP and receive a prescription for an alternative topical therapy.

Patients can receive up to three different topical therapies before being referred by the GP to a specialist review in an outpatient dermatology clinic where second-line treatment options could be considered. Some proportion of these referred patients will be kept on topical therapies, receive support and advice at the review consultation and be discharged back to their GP for long-term management. The remaining proportion will undergo a course of phototherapy and if they respond, they are discharged to their GP for long-term management.

M.2.2.2 Uncertainty

All analyses were conducted probabilistically, thus capturing the imprecision and uncertainty around input parameter point estimates (i.e. mean/median odds ratios, utility weights, etc). A probability

distribution was defined for various model inputs and when the model is run, a value for each input was randomly selected from its specific probability distribution simultaneously and costs and QALYs were calculated using these random values. The model is run repeatedly – in this case 5,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals. In addition, a series of one-way sensitivity analyses were run in order to test the effect of certain structural or variable uncertainties.

M.2.3 Model inputs

M.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 9 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 9: Summary of base-case model inputs

Input	Data	Source
Comparators	See Table 8	
Population	Individuals with mild to moderate chronic plaque psoriasis	
Perspective	UK NHS and & PSS	NICE reference case[63]
Time horizon	1 year	
Discounting	Not applicable (a)	

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

Table 10: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Source/Notes
Baseline Risk (Placebo/vehicle BD)			
Clear/nearly clear	12.5%	Beta: α=116; β=811	Network meta-analysis (see Appendix K)
Efficacy (Odds ratio compared to Baseline)			
Vitamin D OD	5.40	10,000 simulated odds ratios from the NMA were used	Network meta-analysis (see Appendix K)
Vitamin D BD	8.27		Network meta-analysis (see Appendix K)
Potent corticosteroid OD	6.43		Network meta-analysis (see Appendix K)
Potent corticosteroid BD	11.61		Network meta-analysis (see Appendix K)
Combined vitamin D and potent corticosteroid OD	17.09		Network meta-analysis (see Appendix K)
Concurrent vitamin D and potent corticosteroid	13.20		Network meta-analysis (see Appendix K)
Coal Tar BD	8.51		Network meta-analysis (see Appendix K)

Parameter description	Point estimate	Probability distribution	Source/Notes
Dithranol OD	5.23		Network meta-analysis (see Appendix K)
Relapse for all topicals			
All topical therapies	35.5%	Beta: α=192; β= 137	Based on mean from RCTs; test range in sensitivity analysis
Probability of specialist referral and subsequent management			
Referral for specialist review	60%		Dermatology Health Care Needs Assessment [64]
Topicals with specialist advice	70%		Assumption
Treated with phototherapy	30%		Assumption
Probability of response to phototherapy	86.7%	Beta: α=78; β=12	Clinical evidence review for phototherapy (Chapter 9)(Dawe 1998[65]; Hallaji 2010[66]; Cameron 2002[67])
Health-related Quality of Life (a)			
Response - Clear/nearly clear	0.89	See Table 14	Bottomley 2007[62]
Non-response – Not clear/nearly clear	0.85	See Table 14	Assumption
Baseline	0.80	See Table 14	Bottomley 2007[62]
Resource use			
4 weeks of topical treatment			
Vehicle BD	152.8 g	Gamma: α=25.00 β=6.11	Guenther 2002[27]
Vitamin D OD	142.0 g	Gamma: α=25.00 β=5.68	Kaufman 2002[21]
Vitamin D BD	164.9 g	Gamma: α=25.00 β=6.60	Douglas 2002 [38]and Guenther 2002[27]
Potent corticosteroid OD	140.0 g	Gamma: α=25.00 β= 5.60	Kaufman 2002[21]
Potent corticosteroid BD	144.5 g	Gamma: α=25.00 β=5.78	Douglas 2002[38]
Combined vitamin D and potent corticosteroid (TCF product) OD	134.0 g	Gamma: α=25.00 β=5.36	Kaufman 2002[21]
Concurrent vitamin D and potent corticosteroid	160.9 g (80.45 g each)	Gamma: α=25.00 β=6.44	Bottomley 2007[62]
Coal Tar	339.2 g	Gamma: α=25.00 β=13.57	Assumed same as Dithranol

Parameter description	Point estimate	Probability distribution	Source/Notes
Dithranol OD	339.2 g	Gamma: α=25.00 β=13.57	van de Kerkhof 2006[68]
Healthcare consultations			
GP consultation following non-response to topical treatment	1 per treatment change		Bottomley 2007[62] and assumption
Specialist outpatient consultation	1 following failure of 3 topicals		Assumption
Phototherapy sessions	24 per course		Median treatments to clear from phototherapy evidence review (Chapter 9)
Long term management by GP	1 visit per 3 months		Assumption
Cost (£)			
Unit cost of topical treatment			
Vehicle	500 g = £6.32		Diprobase
Vitamin D	100 g = £13.87		100 g Silkis; 120 g Dovonex = £23.10 100 g Curatoderm = £30.86
Potent corticosteroid	100 g = £4.05; 30 g = £1.43		Betnovate cream or ointment 60g Synalar (Fluocinolone acetonide) gel = £10.02 30 g Synalar gel = £5.56
Combined vitamin D and potent corticosteroid (TCF product)	120 g = £61.27; 60 g = £32.99		Dovobet ointment; Dovobet gel: £67.79 (120 g), £36.50 (60 g)
Coal Tar	225 g = £9.42		Psoriderm cream
Dithranol 0.1%	50 g = £3.77		Dithrocream
Dithranol 0.25%	50 g = £4.04		Dithrocream
Dithranol 0.5%	50 g = £4.66		Dithrocream
Dithranol 1%	50 g = £5.42		Dithrocream
Dithranol 2%	50 g = £6.79		Dithrocream
Dithranol 3%	50 g = £16.79		Micanol
Unit cost of healthcare consultations			
GP consultation	£28		PSSRU 2010[69]
Specialist outpatient consultation	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[70]
Specialist outpatient nurse consultation (first visit)	£81	lognormal: log of mean = 4.40 se of logs = 0.03	NHS Reference costs 2009-10[70]

Parameter description	Point estimate	Probability distribution	Source/Notes
Specialist outpatient nurse consultation (follow-up visit)	£64	lognormal: log of mean = 4.15 se of logs = 0.05	NHS Reference costs 2009-10[70]
Phototherapy session (JC29Z)	£82	lognormal: log of mean = 4.40 se of logs = 0.08	NHS Reference costs 2009-10[70]

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

M.2.3.2 Baseline event rates

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

M.2.3.3 Relative treatment effects

In order to estimate the effectiveness for all other comparators in the model, the treatment effect estimates from the network meta-analysis (see Appendix K) were applied to the baseline probabilities outlined above. In the base case, the estimates relating to the investigator assessed outcome (IAGI/PGA) were used. The effect estimates derived from the patient assessed outcome (PAGI) were used in a sensitivity analysis. In a further sensitivity analysis, the data from the network meta-analysis using all available data was used. The odds ratios used in the base case and each sensitivity analysis are presented in Table 11.

Table 11: Treatment effects

	Odds ratio vs placebo (95% CrI)		
Intervention	Base Case	SA – PAGI	SA – all data
Vitamin D OD	5.40 (1.70 to 18.1)	3.30 (0.99 to 11.2)	5.00 (1.85 to 14.0)
Vitamin D BD	8.27 (4.41 to 15.7)	6.50 (2.72 to 16.0)	7.12 (4.05 to 12.4)
Potent corticosteroid OD	6.43 (1.56 to 26.0)	7.76 (1.65 to 39.1)	6.07 (1.75 to 20.8)
Potent corticosteroid BD	11.61 (5.29 to 25.9)	5.54 (1.99 to 16.6)	11.8 (5.76 to 24.5)
TCF OD	17.09 (5.52 to 53.7)	12.9 (4.25 to 41.2)	16.26 (6.45 to 41.2)
Concurrent am/pm	13.2 (3.97 to 47.8)	9.799 (2.18 to 44.6)	11.63 (3.67 to 37.5)
Coal Tar BD	8.51 (2.196 to 35.1)	2.96 (0.81 to 11.3) (a)	4.24 (1.37 to 13.2)
Dithranol OD	5.23 (1.90 to 15.0)	2.96 (0.81 to 11.3)	4.48 (1.70 to 12.1)

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

To calculate the absolute probability of response to a given topical treatment, the odds ratio of that intervention compared to twice daily placebo from the network meta-analysis was converted into a relative risk and applied to the 12.5% baseline risk (e.g. probability of response to twice daily placebo) using the following formula:

$$P_T = P_0 \times RR$$

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

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

Where: OR is the odds ratio of the treatment compared to P_0, the baseline probability. The estimated probabilities of response for the base case and each sensitivity analysis are presented in Table 12.

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

Table 12: Probability of response

	Probabilities of response		
Intervention	Base Case	SA - PAGI	SA - all data
Vehicle BD	12.5%	14.4%	12.5%
Vitamin D OD	43.5%	35.7%	41.7%
Vitamin D BD	54.2%	52.2%	50.4%
Potent corticosteroid OD	47.9%	56.6%	46.4%
Potent corticosteroid BD	62.4%	48.2%	62.8%
TCF OD	70.9%	68.5%	69.9%
Concurrent am/pm	65.3%	62.2%	62.4%
Coal Tar BD	54.9%	33.2%	37.7%
Dithranol OD	42.8%	33.2%	39.0%

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

Early versus late response

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

yet responded, then they are assumed to carry on for a further 4 weeks after which they discontinue having responded or not responded.

On that basis, where data from trials with longer follow-up was available, we looked to estimate what proportion of patients who responded by the end of follow-up had done so within the first 4 weeks or the last 4 weeks. The data with which to estimate this was patchy, but one trial[20] included our main 4 comparators (vehicle, potent corticosteroid, vitamin D analogue and two-compound formulation product) and reported response rates at both 4 weeks and 8 weeks. The data showed that a small proportion of people had responded to vehicle in the first 4 weeks, but by week 8 the number of responders was zero. On that basis, it was assumed that any response to placebo will occur in the first 4 weeks, with no additional responders in the following 8 weeks. For topicals with active ingredients, the data from Fleming 2010 indicated that of all responders to once daily vitamin D analogue at 8 weeks, one-third had achieved clearance by week 4. This figure was 57% and 59% for once daily potent corticosteroids and two-compound formulation product, respectively.

The proportions of early (0 to 4 weeks) and late (5 to 8 weeks) responders from Fleming 2010 were applied to the overall response figures generated from the network meta-analysis in order to estimate the probabilities of response in the first 4 weeks of treatment and the second 4 weeks of treatment (presented in Table 13). In the absence of data, the assumption was made that the proportions of early and late responders is the same for once and twice daily application of a given topical. In other words, this assumes that twice daily application of a topical does not induce response earlier than once daily application of the same topical. This assumption was validated by GDG member experience, which was that frequency of application did not have a demonstrable effect on speed of response.

Table 13: Probabilities of response: overall, early and late

Intervention	Overall probability of achieving response	Of all responders, proportion who will respond in first 4 weeks	Probability of early response (0 to 4 wks)	Probability of late response (5 to 8 wks)
Placebo BD	12.5%	100%	12.5%	0%
Vitamin D OD	43.5%	33%	14.5%	34.0%
Vitamin D BD	54.2%	33%	18.0%	44.1%
Potent corticosteroid OD	47.9%	57%	27.2%	28.4%
Potent corticosteroid BD	62.4%	57%	35.4%	41.7%
TCF OD	70.9%	59%	41.7%	50.1%
Concurrent Vit D and steroid	65.3%	57%	37.1%	44.9%
Coal Tar BD	54.9%	50%	27.4%	37.8%
Dithranol OD	42.8%	50%	21.4%	27.2%

There was no trial data to inform the early compared to late responses for concurrent vitamin D and potent corticosteroid treatment, coal tar or dithranol. In the absence of data, the GDG made the assumption that the proportion of early and late responders to concurrent vitamin D and potent corticosteroid was likely to be the same as for potent steroid given that this is the component most likely to drive rate of response. For dithranol, graphs from Hutchinson 2000[41] were judged to suggest that by the end of week 4, half of overall 8-week improvement in terms of IAGI and PASI had been achieved. Based on this, the assumption was made that the split between early and late response for dithranol was 50/50. Finally, in the absence of data, the GDG made the assumption that the early versus late breakdown for coal tar was the same as for dithranol.

M.2.3.4 Relapse

Psoriasis is a relapsing and remitting chronic condition and achievement of clearance/near clearance with active treatment has no long-term effect on the natural history of chronic plaque psoriasis. The RCT data with regard to relapse was quite sparse and inconsistent, due to a variety of factors including variable trial follow-up and differences in the definition of relapse. For the economic model, the GDG defined relapse as any deterioration to the point at which retreatment is required.

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

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

Referral and specialist management

Sixty percent of hypothetical patients failing to respond to their third topical therapy are assumed to be referred for specialist review. This is based on figures quoted in the Dermatology Health Care Needs Assessment[64], which states that 'although most patients have mild psoriasis, according to Nevitt and Hutchinson[71], 60% had been referred for specialist care at some point.' The 40 percent not referred onward are assumed to be managed by their GP for the time remaining in the model.

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

The 30 percent who receive phototherapy have a probability of responding based up on the results of the clinical evidence review presented in section 9.1 of the full guideline. The clinical evidence shows that around 86.7% of patients who receive a course of narrowband UVB (2 or 3 times weekly) will achieve clearance. For the probabilistic analysis, uncertainty in this estimate of effect was captured using a beta distribution (α=78; β=12).

M.2.3.5 Utilities

Achievement of clearance or near clearance and associated utility gain was used in the model to determine the impact of psoriasis treatment on overall health. Estimates of utility gain were taken from a recent cost-utility analysis included in the health economic review[62]. The mean utility at baseline was 0.8 and mean utility gain associated with clearance/near clearance was 0.09. It is expected that patients who do not achieve clearance or near clearance will still experience some level of improvement on treatment; therefore, these patients also experience a modest utility gain. Bottomley and colleagues modelled a utility gain of 0.07 for non-responders, but the GDG considered this to be optimistic. They felt that the difference between responders and non-responders was

likely to be greater, and therefore recommended a utility gain for non-responders compared to baseline to be slightly less, at 0.05. Due to the uncertainty in this parameter, it was varied in sensitivity analysis.

Table 14: Health state utility values

Health State	Health state utility	Utility loss compared to above health state	Probability distribution for utility loss (a)	Source of health state utility/Notes
Full health	1.00			Anchor state
Response: Clear/nearly clear	0.89	0.11	Gamma: α= 25 β= 227	Bottomley 2007[62]
Non-response: Not clear/nearly clear	0.85	0.04	Gamma: α= 25 β= 625	Assumption Estimate from Bottomley 2007 used in a sensitivity analysis (0.07)
Baseline	0.80	0.05	Gamma: α= 25 β= 500	Bottomley 2007[62]

(a) Utility losses were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically (i.e. such that response was always greater than non-response, which was always greater than baseline). No error estimates were available from the literature, so it was assumed that the standard error (se) of the mean utility loss (m) was 20% of the mean utility loss. α= m^2/se^2; β=se^2/m

Key assumptions about utilities in the model:

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

M.2.3.6 Resource use and cost

Topical therapy

Resource use of alternative topical treatments was based on reported mean quantities of study drugs used by patients in the RCTs[21,27,38,68] at the end of 4-week treatment periods. No estimates were available to inform the mean usage of coal tar used twice daily. In the absence of data, we assumed that the mean usage for coal tar would be approximately equal to that of dithranol. No estimate from an RCT was available to inform the mean quantities of vitamin D analogue and potent corticosteroid when they are used concurrently (e.g. one in the morning and the other in the evening). In the cost-utility analysis by Bottomley and colleagues[62], they estimated mean usage for this strategy to be 160.9 g (95% CI: 140.7-181.1) based on an unpublished trial they held on file. We have taken this estimate for use in our model, assuming that the total usage is split evenly between vitamin D analogue and potent corticosteroid. Mean quantities and distribution parameters for the probabilistic analysis are presented in Table 15.

Unit costs of topicals (Table 16) were taken from the most recent BNF[72]. Given that the interventions were modelled assuming a class effect, the cost of topical had to be selected from a variety of compounds, formulations and package sizes. For simplicity, we used the cost for the topical with the lowest unit cost per gram/millilitre.

Table 15: Mean quantities of topicals used per 4-week cycle

Topical therapy	Mean quantity used	Probability distribution	Source/Notes
Vehicle BD	152.8 g	Gamma: α=25.00 β=6.11	Guenther 2002[27]
Vitamin D OD	142.0 g	Gamma: α=25.00 β=5.68	Kaufman 2002[21]
Vitamin D BD	164.9 g	Gamma: α=25.00 β=6.60	Douglas 2002[38] and Guenther 2002[27]
Potent corticosteroid OD	140.0 g	Gamma: α=25.00 β= 5.60	Kaufman 2002[21]
Potent corticosteroid BD	144.5 g	Gamma: α=25.00 β=5.78	Douglas 2002[38]
Combined vitamin D and potent corticosteroid (TCF product) OD	134.0 g	Gamma: α=25.00 β=5.36	Kaufman 2002[21]
Concurrent vitamin D and potent corticosteroid	160.9 g (80.45 g each)	Gamma: α=25.00 β=6.44	Bottomley 2007[62]
Coal Tar	339.2 g	Gamma: α=25.00 β=13.57	Assumed same as Dithranol
Dithranol OD	339.2 g	Gamma: α=25.00 β=13.57	van de Kerkhof 2006[68]

Table 16: Unit costs of topical therapies

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

Topical therapy	Unit cost (£)	Source/Notes
Dithranol 0.5%	50 g = £4.66	Dithrocream
Dithranol 1%	50 g = £5.42	Dithrocream

To calculate the per cycle cost of each topical, the mean quantities were converted into the cheapest combination of the number of packs of topical needed. For example, the mean 4-week dosage for twice daily potent corticosteroids was 144.5 g. The cheapest combination of packs needed to provide this quantity was one 100 g pack and two 30 g packs. The 4-week costs of topical treatment based on the mean quantities used are presented in Table 17.

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

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

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

Table 17: Mean cost of 4-week topical treatment

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

Health care consultations

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

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

Each patient who is referred is seen by a consultant dermatologist in an outpatient clinic, thus accruing this cost. Based on GDG experience, it was assumed that 70% of these referred patients will be kept on topical therapies, receive support and advice at the review consultation and be discharged back to their GP for long-term management. The other 30% are assumed to undergo a course of phototherapy, thus accruing the cost of 24 sessions of narrowband UVB. Responders to narrowband UVB are assumed to be discharged to their GP for long-term management; non-responders are assumed to be managed in long-term specialist care.

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

Table 18: Unit cost of health care consultations

Type of health care consultation	Health care resource use	Unit cost per consultation	Probability distribution	Source/Notes
GP consultation	1 per treatment change 1 visit per 3 months for long term management	£28		PSSRU 2010[69]
Specialist outpatient consultation	1 following failure of 3 topicals	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[70]
Specialist outpatient nurse consultation (first visit)	1 following failure of 3 topicals	£81	lognormal: log of mean = 4.40 se of logs = 0.03	NHS Reference costs 2009-10[70]
Phototherapy session (JC29Z)	24 sessions per course	£82	lognormal: log of mean = 4.40 se of logs = 0.08	NHS Reference costs 2009-10[70]

M.2.4 Computations

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

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

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

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

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

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

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

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

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

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

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

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

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

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

M.2.5 Sensitivity analyses

A series of one-way sensitivity analyses and scenario analyses were performed to assess how changes in one or more parameters or assumptions might change the conclusions of the analysis. In one set of sensitivity analyses, alternative estimates of treatment effects from the network meta-analyses (Appendix K) were used. In a second sensitivity analysis, the utility value associated with non-response was varied upward to match the estimate used by Bottomley and colleagues[62]. In a third set of sensitivity analyses, the quantity of TCF product used over a 4 week treatment period was reduced to match the estimate used by Bottomley and colleagues. In a fourth series of sensitivity analyses, estimates of future resource use and cost were altered and the time horizon was lengthened. Finally, alternative assumptions about the comparators were used to explore what might be appropriate if there were concerns about safety or contraindications.

M.2.6 Model validation

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

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

M.3 Results

M.3.1 Base case

This analysis found that, given a NICE willingness-to-pay threshold of £20,000 per QALY gained, the most cost-effective strategy is likely to be one of starting with twice daily potent corticosteroid and moving to concurrent potent corticosteroid and vitamin D analogue and then twice daily coal tar. This strategy was also the least costly strategy among the 118 modelled. Base case results for non-dominated and non-extendedly dominated strategies are presented in Table 19.

Results showed that starting with concurrent potent corticosteroid and vitamin D analogue and switching to twice daily potent corticosteroid and then twice daily coal tar is £9 more costly over 1 year and only produces 0.00041 more QALYs than the least costly strategy mentioned above. This gives it an incremental cost-effectiveness ratio (ICER) of £22,658 which is just above the NICE £20,000 per QALY threshold.

The most effective strategy (once daily TCF then twice daily potent corticosteroid then twice daily coal tar) costs an additional £192 per year compared to the next most costly non-dominated strategy (concurrent steroid and vitamin D then twice daily potent steroid then twice daily coal tar), yet produces just 0.00107 additional QALYs for an ICER of over £179,000. Based on the results of this model, it appears that starting with once daily TCF, although most effective, is very unlikely to be cost-effective.

Table 19: Incremental analysis of base case results – psoriasis of trunk and limbs

Strategy (a)	Cost	Incremental Cost	Benefit (QALYs)	Incremental Benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	Probability most cost effective at £20k threshold (b)
PS BD - Concurrent - Coal Tar BD	£226.50		0.84872			22%
Concurrent - PS BD - Coal tar BD	£235.80	£9.30	0.84913	0.00041	£22,658	22%
TCF OD - PS BD - Coal Tar BD	£427.80	£192.00	0.85020	0.00107	£179,439	0%

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

(b) Strategies not on the cost-effectiveness frontier but with high likelihood of being cost effective include PS BD – Concurrent – Vit D BD and Concurrent – PS BD – Vit D BD (optimal in 12% and 13% of simulations and ranked third and fourth in terms of NMB, respectively)

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

that a strategy of using vehicle or emollient with no active agent only was the most costly and least effective, largely driven by the cost of referrals and specialist management for non-responders. Strategies that included once or twice daily vitamin D were not cost-effective regardless of where they were included in the sequence. This is largely due to their relatively low rank in terms of effectiveness and their relatively high acquisition cost. Strategies that included dithranol were also all dominated, that is more costly and less effective than alternatives. Finally, strategies in which patients were referred after non-response to only 2 topicals were all dominated, thus not cost effective.

A breakdown of total costs by type of resource use (i.e. topicals, GP visits, outpatient consultations, phototherapy) is presented for all modelled strategies in Table 21. Note that these costs were produced by a deterministic run of the model and therefore may not match exactly the total costs presented from the probabilistic analysis in Table 20; however, they are very similar. Disaggregation of costs allows one to observe what part of a given strategy is driving the majority of total cost. Strategies that are less effective tend to have higher downstream costs driven by visits to the GP and referrals for specialist review and/or phototherapy. Strategies that are very effective are likely to have lower downstream costs, but potentially higher drug costs. Based on this disaggregation, it becomes clear that strategies with TCF product or vitamin D analogue have relatively high topical costs, some of which are offset by reduced downstream costs in terms of consultations with specialists and courses of phototherapy. Strategies with potent corticosteroids offered alone or in combination with vitamin D analogue (concurrent therapy) show similar downstream costs as strategies involving TCF product, but because their acquisition cost is dramatically lower, the overall total cost is much lower.

The probabilistic analysis indicates that there is a great deal of uncertainty as to which sequence is optimal (i.e. most cost effective). There appears to be very little difference between initial potent corticosteroid followed by concurrent corticosteroid and vitamin D and vice versa, with the difference in their net monetary benefits (NMB) being only £1 (£16,748 and £16,747 respectively) and both having an equal probability of being optimal at a £20,000 willingness to pay threshold. Generally, it looks as though a strategy of starting with either potent corticosteroids or concurrent treatment with potent corticosteroid and vitamin D analogue is most likely to be cost-effective, whereas starting with once daily TCF product is very unlikely to be cost-effective.

Table 20: Mean total costs and QALYs for all modelled comparators

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @£20k
PS BD - Concurrent - Coal Tar BD	226	109	to	404	0.8487	0.8022	to	0.8877	16748
Concurrent - PS BD - Coal tar BD	236	125	to	407	0.8491	0.8024	to	0.8886	16747
PS BD - Concurrent - Vit D BD	238	117	to	412	0.8486	0.8019	to	0.8875	16735
Concurrent - PS BD - Vit D BD	247	133	to	415	0.8490	0.8022	to	0.8885	16734
PS BD - Vit D BD - Concurrent	255	137	to	420	0.8483	0.8015	to	0.8874	16712
Concurrent - Vit D BD - PS BD	272	150	to	435	0.8488	0.8021	to	0.8884	16705
PS BD - Concurrent - Dithranol OD	267	127	to	466	0.8483	0.8016	to	0.8875	16699
Concurrent - PS BD - Dithranol OD	276	140	to	467	0.8487	0.8021	to	0.8884	16698
PS BD - Vit D OD - Concurrent	268	139	to	450	0.8479	0.8014	to	0.8871	16690
PS OD - PS BD - Coal Tar BD	249	110	to	431	0.8466	0.8004	to	0.8861	16682

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @£20k
PS BD - Vit D BD - Coal Tar BD	279	147	to	449	0.8478	0.8009	to	0.8871	16678
Vit D BD - PS BD - Concurrent	276	178	to	422	0.8476	0.8008	to	0.8870	16676
Concurrent - Vit D BD - Coal Tar BD	301	158	to	498	0.8485	0.8017	to	0.8881	16669
PS OD - Concurrent - Coal tar BD	269	115	to	484	0.8468	0.8004	to	0.8862	16667
Vit D BD - Concurrent - PS BD	289	190	to	436	0.8477	0.8010	to	0.8870	16665
PS OD - PS BD - Vit D BD	264	122	to	441	0.8464	0.8002	to	0.8859	16665
PS BD - Vit D BD - TCF OD	319	172	to	510	0.8487	0.8019	to	0.8877	16654
PS BD - Vit D OD - Coal Tar BD	295	151	to	471	0.8474	0.8007	to	0.8865	16652
PS OD - Concurrent - Vit D BD	284	123	to	493	0.8467	0.8002	to	0.8860	16650
Concurrent - Vit D BD - TCF OD	339	175	to	561	0.8493	0.8028	to	0.8888	16646
Vit D OD - PS BD - Concurrent	285	173	to	452	0.8465	0.8004	to	0.8859	16645
Vit D BD - PS BD - Coal Tar BD	300	187	to	453	0.8471	0.8003	to	0.8862	16642
PS BD - Vit D OD - Vit D BD	310	165	to	487	0.8472	0.8003	to	0.8865	16635
PS OD - PS BD - Vit D OD	285	117	to	483	0.8460	0.7994	to	0.8856	16634
Vit D OD - Concurrent - PS BD	299	185	to	464	0.8466	0.8004	to	0.8859	16633
Vit D BD - PS OD - PS BD	302	187	to	454	0.8467	0.8000	to	0.8861	16631
PS OD - Vit D BD - PS BD	294	149	to	461	0.8462	0.7998	to	0.8856	16630
PS BD - TCF OD - Coal Tar BD	353	197	to	545	0.8492	0.8027	to	0.8881	16630
Vit D BD - Concurrent - Coal tar BD	318	199	to	497	0.8474	0.8008	to	0.8866	16629
Vit D BD - PS OD - Concurrent	311	182	to	491	0.8468	0.8000	to	0.8860	16625
PS OD - Vit D BD - Concurrent	303	145	to	498	0.8464	0.7999	to	0.8856	16625
Concurrent - TCF OD - Coal tar BD	371	194	to	601	0.8497	0.8032	to	0.8891	16624
PS BD - Vit D OD - TCF OD	342	175	to	555	0.8482	0.8017	to	0.8873	16622
Vit D BD - PS BD - TCF OD	339	214	to	513	0.8479	0.8014	to	0.8871	16620
PS BD - Vit D BD - Dithranol OD	328	172	to	520	0.8473	0.8002	to	0.8869	16618
PS OD - PS BD - Dithranol OD	302	138	to	498	0.8460	0.7994	to	0.8855	16618
PS BD - TCF OD - Vit D BD	364	204	to	554	0.8491	0.8023	to	0.8880	16618
Concurrent - Vit D BD - Dithranol OD	347	175	to	558	0.8480	0.8014	to	0.8877	16614
Concurrent - TCF OD - Vit D BD	381	197	to	610	0.8497	0.8030	to	0.8892	16612
PS BD - Concurrent - Referral	335	161	to	548	0.8472	0.8004	to	0.8864	16609
Concurrent - PS BD - Referral	344	176	to	551	0.8476	0.8006	to	0.8874	16608
Vit D OD - PS BD - Coal tar OD	311	184	to	474	0.8460	0.7999	to	0.8854	16608
Vit D BD - Concurrent - TCF OD	356	216	to	560	0.8481	0.8014	to	0.8874	16606

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @£20k
PS OD - Concurrent - Dithranol OD	320	134	to	556	0.8463	0.7996	to	0.8856	16606
PS OD - Vit D OD - PS BD	311	139	to	500	0.8456	0.7992	to	0.8854	16602
PS OD - Vit D OD - Concurrent	323	134	to	557	0.8458	0.7992	to	0.8851	16593
Vit D OD - Concurrent - Coal tar BD	332	193	to	537	0.8462	0.8000	to	0.8857	16592
Vit D OD - PS BD - Vit D BD	327	202	to	487	0.8458	0.7995	to	0.8854	16589
Vit D OD - PS OD - PS BD	318	177	to	493	0.8454	0.7991	to	0.8849	16589
PS BD - TCF OD - Dithranol OD	389	214	to	599	0.8488	0.8019	to	0.8880	16587
PS BD - Vit D OD - Dithranol OD	350	181	to	545	0.8468	0.7998	to	0.8863	16586
Vit D BD - PS OD - Coal Tar BD	340	198	to	525	0.8462	0.7999	to	0.8856	16584
Vit D BD - PS BD - Dithranol OD	348	217	to	521	0.8466	0.7996	to	0.8861	16584
PS OD - Vit D BD - Coal Tar BD	332	156	to	531	0.8458	0.7993	to	0.8853	16584
Concurrent - TCF OD - Dithranol OD	405	205	to	658	0.8494	0.8028	to	0.8890	16582
Vit D OD - PS OD - Concurrent	330	172	to	549	0.8455	0.7991	to	0.8849	16581
Vit D OD - PS BD - TCF OD	359	209	to	556	0.8468	0.8005	to	0.8863	16577
TCF OD - PS BD - Coal Tar BD	428	290	to	575	0.8502	0.8041	to	0.8894	16576
Vit D OD - Concurrent - Vit D BD	347	201	to	540	0.8461	0.7996	to	0.8855	16575
Vit D BD - Concurrent - Dithranol OD	364	217	to	557	0.8469	0.8004	to	0.8864	16574
TCF OD - PS BD - Vit D BD	438	300	to	581	0.8501	0.8038	to	0.8892	16564
Vit D OD - Concurrent - TCF OD	379	207	to	625	0.8470	0.8009	to	0.8863	16561
Vit D OD - Vit D BD - PS BD	357	236	to	505	0.8456	0.7994	to	0.8852	16555
Vit D BD - PS OD - TCF OD	391	217	to	611	0.8471	0.8006	to	0.8863	16552
PS OD - Vit D BD - TCF OD	383	177	to	620	0.8467	0.8000	to	0.8859	16551
Vit D OD - Vit D BD - Concurrent	367	230	to	545	0.8458	0.7993	to	0.8853	16548
PS OD - Vit D OD - Coal tar BD	355	148	to	582	0.8451	0.7989	to	0.8849	16548
Vit D OD - PS BD - Dithranol OD	366	217	to	547	0.8454	0.7989	to	0.8851	16541
TCF OD - Vit D BD - PS BD	461	322	to	602	0.8499	0.8035	to	0.8892	16538
Vit D OD - PS OD - Coal tar BD	362	185	to	575	0.8449	0.7987	to	0.8845	16535
TCF OD - PS BD - Dithranol OD	463	310	to	624	0.8498	0.8034	to	0.8889	16533
Vit D BD - TCF OD - PS BD	432	296	to	590	0.8482	0.8016	to	0.8872	16531
Vit D OD - Concurrent - Dithranol OD	385	213	to	604	0.8457	0.7991	to	0.8852	16528
PS OD - Vit D OD - Vit D BD	375	162	to	588	0.8450	0.7984	to	0.8847	16525
PS OD - TCF OD - Coal Tar BD	421	200	to	660	0.8473	0.8007	to	0.8868	16524

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @£20k
Concurrent - Vit D BD - Referral	421	218	to	643	0.8468	0.7998	to	0.8866	16515
PS BD - Vit D BD - referral	407	233	to	592	0.8460	0.7989	to	0.8855	16513
Vit D OD - PS OD - Vit D BD	381	200	to	580	0.8447	0.7985	to	0.8842	16513
Vit D BD - PS OD - Dithranol OD	400	233	to	590	0.8456	0.7989	to	0.8852	16512
PS OD - Vit D BD - Dithranol OD	392	191	to	598	0.8452	0.7983	to	0.8847	16511
PS OD - TCF OD - Vit D BD	434	207	to	670	0.8472	0.8004	to	0.8864	16509
TCF OD - Vit D BD - Coal Tar BD	486	331	to	650	0.8496	0.8035	to	0.8888	16507
PS BD - TCF OD - Referral	450	254	to	672	0.8478	0.8012	to	0.8870	16507
Concurrent - TCF OD - Referral	463	232	to	743	0.8485	0.8013	to	0.8880	16506
Vit D OD - Vit D BD - Coal Tar BD	397	248	to	574	0.8451	0.7990	to	0.8846	16506
PS OD - Vit D OD - TCF OD	417	161	to	719	0.8461	0.7994	to	0.8857	16505
PS OD - PS BD - Referral	387	190	to	583	0.8446	0.7979	to	0.8844	16505
PS OD - Concurrent - Referral	399	169	to	649	0.8450	0.7980	to	0.8845	16500
Vit D BD - TCF OD - Coal Tar BD	458	307	to	641	0.8479	0.8013	to	0.8869	16499
Vit D OD - Vit D BD - PS OD	401	235	to	589	0.8447	0.7983	to	0.8842	16494
Vit D OD - PS OD - TCF OD	424	201	to	711	0.8459	0.7996	to	0.8851	16493
Vit D OD - TCF OD - PS BD	458	291	to	638	0.8470	0.8009	to	0.8865	16483
Vit D BD - PS BD - Referral	428	279	to	592	0.8453	0.7983	to	0.8847	16478
Vit D BD - Concurrent - Referral	438	262	to	643	0.8457	0.7989	to	0.8854	16476
Vit D OD - Vit D BD - TCF OD	450	273	to	660	0.8461	0.7999	to	0.8855	16472
PS OD - TCF OD - Dithranol OD	466	214	to	730	0.8468	0.7999	to	0.8860	16470
PS BD - Vit D OD - Referral	437	248	to	628	0.8453	0.7986	to	0.8850	16469
PS OD - Vit D OD - Dithranol OD	424	175	to	672	0.8444	0.7979	to	0.8842	16464
TCF OD - Vit D BD - Dithranol OD	526	354	to	701	0.8492	0.8026	to	0.8884	16458
TCF OD - PS BD - Referral	525	352	to	698	0.8489	0.8024	to	0.8882	16452
Vit D OD - PS OD - Dithranol OD	431	217	to	664	0.8441	0.7976	to	0.8838	16452
Vit D BD - TCF OD - Dithranol OD	498	330	to	694	0.8474	0.8008	to	0.8869	16451
Vit D OD - TCF OD - Coal Tar BD	488	300	to	704	0.8467	0.8008	to	0.8862	16446
Vit D OD - Vit D BD - Dithranol OD	459	288	to	644	0.8445	0.7981	to	0.8842	16431
Vit D OD - TCF OD - Vit D BD	502	308	to	709	0.8466	0.8004	to	0.8859	16430
Vit D OD - PS BD - Referral	454	283	to	629	0.8439	0.7975	to	0.8839	16424

Strategy (a)	Mean Cost (£)	95% CI (£)			Mean Benefit (QALYs)	95% CI (QALYs)			Mean NMB @£20k
Vit D OD - Concurrent - Referral	467	253	to	697	0.8443	0.7975	to	0.8839	16418
Vit D OD - TCF OD - Dithranol OD	535	317	to	771	0.8462	0.7997	to	0.8855	16389
Vit D BD - PS OD - Referral	492	293	to	672	0.8440	0.7974	to	0.8837	16388
PS OD - Vit D BD - Referral	484	251	to	680	0.8436	0.7968	to	0.8834	16387
PS OD - TCF OD - Referral	540	244	to	831	0.8456	0.7988	to	0.8853	16371
TCF OD - Vit D BD - Referral	594	399	to	777	0.8481	0.8015	to	0.8875	16369
Vit D BD - TCF OD - Referral	565	375	to	773	0.8464	0.7999	to	0.8859	16362
PS OD - Vit D OD - Referral	526	228	to	764	0.8426	0.7956	to	0.8827	16325
Vit D OD - PS OD - Referral	533	270	to	757	0.8423	0.7954	to	0.8823	16313
Vit D OD - Vit D BD - Referral	554	366	to	721	0.8428	0.7963	to	0.8829	16303
Vit D OD - TCF OD - Referral	611	352	to	867	0.8449	0.7986	to	0.8844	16288
Vehicle only	664	605	to	727	0.8358	0.7887	to	0.8758	16052

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

Table 21: Disaggregated total costs by items of resource use

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

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
PS BD - Vit D OD - Vit D BD	£151	£53	£20	£83	£307
PS OD - PS BD - Vit D OD	£112	£58	£22	£94	£286
Vit D OD - Concurrent - PS BD	£157	£53	£16	£68	£294
Vit D BD - PS OD - PS BD	£140	£55	£19	£79	£293
PS OD - Vit D BD - PS BD	£134	£57	£19	£79	£289
PS BD - TCF OD - Coal Tar BD	£268	£41	£12	£49	£370
Vit D BD - Concurrent - Coal tar BD	£172	£49	£16	£66	£303
Vit D BD - PS OD - Concurrent	£154	£54	£18	£74	£300
PS OD - Vit D BD - Concurrent	£148	£56	£18	£74	£296
Concurrent - TCF OD - Coal tar BD	£289	£39	£11	£46	£385
PS BD - Vit D OD - TCF OD	£232	£48	£14	£58	£352
Vit D BD - PS BD - TCF OD	£230	£46	£12	£49	£337
PS BD - Vit D BD - Dithranol OD	£158	£51	£20	£84	£313
PS OD - PS BD - Dithranol OD	£123	£58	£23	£96	£300
PS BD - TCF OD - Vit D BD	£276	£41	£12	£49	£378
Concurrent - Vit D BD - Dithranol OD	£184	£49	£19	£79	£331
Concurrent - TCF OD - Vit D BD	£297	£39	£11	£46	£393
PS BD - Concurrent - Referral	£128	£48	£28	£126	£330
Concurrent - PS BD - Referral	£137	£47	£28	£126	£338
Vit D OD - PS BD - Coal tar OD	£150	£57	£20	£84	£311
Vit D BD - Concurrent - TCF OD	£249	£45	£11	£46	£351
PS OD - Concurrent - Dithranol OD	£147	£56	£21	£90	£314
PS OD - Vit D OD - PS BD	£137	£62	£22	£94	£315
PS OD - Vit D OD - Concurrent	£153	£61	£21	£88	£323
Vit D OD - Concurrent - Coal tar BD	£176	£55	£19	£78	£328
Vit D OD - PS BD - Vit D BD	£163	£57	£20	£83	£323
Vit D OD - PS OD - PS BD	£140	£62	£22	£94	£318
PS BD - TCF OD - Dithranol OD	£286	£43	£14	£59	£402
PS BD - Vit D OD - Dithranol OD	£167	£56	£23	£100	£346
Vit D BD - PS OD - Coal Tar BD	£163	£58	£22	£92	£335
Vit D BD - PS BD - Dithranol OD	£174	£53	£20	£84	£331
PS OD - Vit D BD - Coal Tar BD	£157	£59	£22	£92	£330
Concurrent - TCF OD - Dithranol OD	£306	£41	£13	£55	£415
Vit D OD - PS OD - Concurrent	£156	£61	£21	£88	£326
Vit D OD - PS BD - TCF OD	£244	£52	£14	£58	£368
TCF OD - PS BD - Coal Tar BD	£356	£38	£12	£49	£455
Vit D OD - Concurrent - Vit D BD	£189	£55	£19	£78	£341
Vit D BD - Concurrent - Dithranol OD	£196	£51	£19	£79	£345
TCF OD - PS BD - Vit D BD	£364	£38	£12	£49	£463
Vit D OD - Concurrent - TCF OD	£265	£51	£13	£54	£383
Vit D OD - Vit D BD - PS BD	£191	£59	£20	£83	£353
Vit D BD - PS OD - TCF OD	£265	£52	£15	£64	£396

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
PS OD - Vit D BD - TCF OD	£259	£54	£15	£64	£392
Vit D OD - Vit D BD - Concurrent	£205	£58	£19	£78	£360
PS OD - Vit D OD - Coal tar BD	£164	£65	£25	£109	£363
Vit D OD - PS BD - Dithranol OD	£180	£60	£23	£100	£363
TCF OD - Vit D BD - PS BD	£384	£39	£12	£49	£484
Vit D OD - PS OD - Coal tar BD	£167	£65	£25	£109	£366
TCF OD - PS BD - Dithranol OD	£374	£40	£14	£59	£487
Vit D BD - TCF OD - PS BD	£341	£44	£12	£49	£446
Vit D OD - Concurrent - Dithranol OD	£204	£58	£22	£94	£378
PS OD - Vit D OD - Vit D BD	£180	£65	£25	£108	£378
PS OD - TCF OD - Coal Tar BD	£322	£50	£16	£64	£452
Concurrent - Vit D BD - Referral	£190	£50	£31	£142	£413
PS BD - Vit D BD - referral	£164	£53	£33	£151	£401
Vit D OD - PS OD - Vit D BD	£183	£65	£25	£108	£381
Vit D BD - PS OD - Dithranol OD	£195	£61	£26	£110	£392
PS OD - Vit D BD - Dithranol OD	£189	£63	£26	£110	£388
PS OD - TCF OD - Vit D BD	£332	£50	£15	£64	£461
TCF OD - Vit D BD - Coal Tar BD	£399	£41	£14	£57	£511
PS BD - TCF OD - Referral	£290	£44	£25	£110	£469
Concurrent - TCF OD - Referral	£310	£42	£23	£103	£478
Vit D OD - Vit D BD - Coal Tar BD	£215	£61	£23	£96	£395
PS OD - Vit D OD - TCF OD	£281	£58	£18	£76	£433
PS OD - PS BD - Referral	£130	£60	£37	£168	£395
PS OD - Concurrent - Referral	£153	£58	£35	£158	£404
Vit D BD - TCF OD - Coal Tar BD	£356	£46	£14	£57	£473
Vit D OD - Vit D BD - PS OD	£202	£63	£25	£108	£398
Vit D OD - PS OD - TCF OD	£284	£59	£18	£76	£437
Vit D OD - TCF OD - PS BD	£366	£50	£14	£58	£488
Vit D BD - PS BD - Referral	£180	£55	£33	£151	£419
Vit D BD - Concurrent - Referral	£202	£53	£31	£142	£428
Vit D OD - Vit D BD - TCF OD	£320	£56	£16	£67	£459
PS OD - TCF OD - Dithranol OD	£345	£52	£18	£77	£492
PS BD - Vit D OD - Referral	£174	£58	£38	£174	£444
PS OD - Vit D OD - Dithranol OD	£201	£69	£30	£130	£430
TCF OD - Vit D BD - Dithranol OD	£420	£43	£16	£68	£547
TCF OD - PS BD - Referral	£378	£41	£25	£110	£554
Vit D OD - PS OD - Dithranol OD	£204	£69	£30	£130	£433
Vit D BD - TCF OD - Dithranol OD	£377	£48	£16	£68	£509
Vit D OD - TCF OD - Coal Tar BD	£384	£51	£16	£67	£518
Vit D OD - Vit D BD - Dithranol OD	£248	£65	£27	£115	£455
Vit D OD - TCF OD - Vit D BD	£394	£51	£16	£67	£528
Vit D OD - PS BD - Referral	£187	£62	£38	£174	£461

Strategy	Topicals	Primary Care	Specialist Outpatient	Phototherapy	Total (a)
Vit D OD - Concurrent - Referral	£211	£60	£36	£164	£471
Vit D OD - TCF OD - Dithranol OD	£408	£54	£19	£81	£562
Vit D BD - PS OD - Referral	£203	£64	£41	£189	£497
PS OD - Vit D BD - Referral	£197	£65	£41	£189	£492
PS OD - TCF OD - Referral	£350	£54	£31	£139	£574
TCF OD - Vit D BD - Referral	£424	£44	£28	£124	£620
Vit D BD - TCF OD - Referral	£381	£49	£28	£124	£582
PS OD - Vit D OD - Referral	£211	£72	£47	£217	£547
Vit D OD - PS OD - Referral	£214	£72	£47	£217	£550
Vit D OD - Vit D BD - Referral	£256	£67	£42	£195	£560
Vit D OD - TCF OD - Referral	£413	£56	£32	£144	£645
Vehicle only	£178	£117	£63	£309	£667

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

M.3.2 Sensitivity analyses

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

M.3.2.1 Treatment effects

The network meta-analysis of topical therapies was performed for two response outcomes: investigator assessed global improvement (IAGI) and patient assessed global improvement (PAGI). The economic evaluation used the investigator assessed outcome in the base case, largely because there was more data from the randomised evidence reported for this outcome. In a sensitivity analysis, treatment effects from the network meta-analysis of patient reported outcome was used. Results of this sensitivity analysis are presented in Table 22.

Table 22: Incremental analysis of sensitivity analysis using patient-reported outcome (PAGI)

Strategy (a)	Cost	Incremental Cost	Benefit (QALYs)	Incremental benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold (b)
PS OD - Concurrent - Vit D BD	£275.50		0.84774			£16,679	34%
Concurrent - Vit D BD - TCF OD	£370.50	£86.90	0.84867	0.00093	£102,151	£16,603	3%
Concurrent - TCF OD - Vit D BD	£410.80	£40.30	0.84902	0.00035	£115,143	£16,570	0%

(a) All sequences not presented here were ruled out through dominance (more costly and less effective than a strategy included in the table) or extended dominance (more costly and less effective than a mixture of two other strategies included in the table)
(b) Strategies not on the cost-effectiveness frontier but with high likelihood of being cost effective include Concurrent – PS BD – Vit D BD (optimal in 23% of simulations)

Results of the analysis using patient reported outcomes indicates that starting treatment with once daily potent corticosteroids, moving on the concurrent treatment if that fails and then trying twice daily vitamin D analogue is likely to be both the least costly and most cost-effective strategy given a threshold of £20,000 per QALY gained. Initial treatment with concurrent potent corticosteroid and vitamin D analogue appears less cost-effective using patient reported outcomes than physician reported outcomes, unlikely to be cost-effective at thresholds less than £100,000. Once daily TCF product, first or second line in a sequence, still looks to generate additional benefits (QALYs), but at additional costs unlikely to be considered good value for NHS resource (ICERs upwards of £115,000 per QALY gained).

The base case network meta-analysis of physician/investigator assessed response used in the base case cost-effectiveness analysis included all RCTs that met the inclusion criteria for the clinical review of direct evidence. The review of direct evidence was quite focused and as such did not include evidence for every possible pair wise comparison. In a sensitivity analysis of the network meta-analysis and thus the cost-effectiveness analysis, additional studies were included. For details on the particulars of these sensitivity analyses and what effect they had on the estimated treatment effects, see Appendix K.

When treatment effects were based on all relevant RCT data, the results of the base case changed only slightly. Twice daily potent corticosteroid followed by concurrent steroid and vitamin D analogue is still likely to be optimal for first and second line treatments. However, instead of twice daily coal representing the optimal third line topical, twice daily vitamin D analogue looks to be most cost-effective. This sensitivity analysis calls into question whether vitamin D or coal tar represents the better third line treatment option.

M.3.2.2 Variation in early versus late response

The base case assumed that patients would trial a given topical for up to 8 weeks and that some proportion of patients would be expected to respond by 4 weeks and discontinue treatment at that time. The remainder would carry on to 8 weeks, at which time non-responders would move on to the next topical in a sequence. The data defining the breakdown of early (at 4 weeks) vs late (at 8 weeks) responders was limited to two studies[41,73] and GDG opinion and was thus very uncertain. Deterministic sensitivity analyses were performed around these parameters to observe the impact on the results.

First, an analysis was performed in which no one was expected to respond and discontinue treatment at 4 weeks (i.e. all responders require 8 weeks treatment). Compared to the results of the base case when all comparators are included, the rank order of strategies in terms of mean net benefits changed very little. The ICERs for strategies on the cost-effectiveness frontier (see Table 19) increased relative to the base case, thus becoming less likely to be considered cost-effective.

Second, an analysis was performed in which all responders were assumed to respond by 4 weeks, with no one requiring an additional 4 weeks of treatment. The ICER for all strategies on the cost-effectiveness plane (see Table 19) decreased relative to the base case, and now starting with concurrent therapy and moving to twice daily potent corticosteroids looks to be cost-effective at a £20,000 threshold compared to potent corticosteroids and then concurrent therapy. Initial treatment with once daily TCF product is still unlikely to be cost-effective, with an ICER of more than £140,000.

Finally, an analysis was performed in which a 4-week stopping rule was applied. In this scenario, responders were limited to those that have responded by week 4 (see Table 13), and all other patients are assumed to move on to the next topical in the sequence (i.e. no one continues to 8 weeks of treatment with the same topical). Relative to the base case, the total costs for all strategies more than doubled as more patients were classified as non-responders and moved down the care pathway reaching referral to secondary care. Starting with concurrent therapy and then moving to twice daily potent corticosteroids was now the least costly strategy and most likely to be cost-effective. The ICER for once daily TCF product instead of concurrent therapy in this sequence decreased substantially relative to the base case (£174,000 to £94,000) but is still unlikely to be considered cost-effective at the NICE threshold.

M.3.2.3 Reduced adherence

There was some concern that issues of treatment adherence were inadequately captured in the model. The estimates of effect used in the base case were derived from randomised controlled trials which may represent the best case scenario for topical therapies. The GDG wished to explore how reduced adherence to twice daily treatments would affect the conclusions of the base case. In this scenario, 60% of patients being treated with twice daily topical were assumed to adhere to twice daily treatment whilst the remaining 40% of patients were assumed to apply the topical only once daily[74]. For concurrent therapy, the 40% were assumed to adhere to once daily potent corticosteroid treatment only. Efficacy of the twice daily treatments would thus be reduced compared to the base case estimates. To be conservative, no reductions in cost were assumed despite the fact that less topical would be used.

With adherence reduced, there is no change substantive change to the results of the base case. Total costs across all strategies increase slightly (average of £27 more) and benefits decreased very slightly (average of 0.0007 fewer QALYs), but the conclusions from the base case remain unchanged. The most cost-effective strategy, given a £20,000 per additional QALY threshold is still twice daily potent corticosteroid followed by concurrent therapy and then twice daily coal tar. To put concurrent therapy before twice daily potent corticosteroids has an ICER of £36,000 (up from £23,000 in base case) and to replace concurrent therapy with once daily TCF before steroids has an ICER of £76,609 (down from £174,545 in the base case).

M.3.2.4 Utility values

In the base case, the mean utility gain associated with achieving some level of improvement, but not clearance or near clearance was assumed to be 0.05. This value was based on a downward adjustment of a value used in a recent cost-utility analysis included in the health economic review. Bottomley and colleagues[62] modelled a utility gain of 0.07 for non-responders compared to baseline. To see what effect the GDG adjustment had on the results, the Bottomley figure (0.07) was used in a sensitivity analysis

Results indicate that the conclusion about cost-effectiveness changes very little using this more optimistic estimate of utility gain. The ICERs for all strategies increases relative to the base case; therefore, starting with concurrent treatment before twice daily potent corticosteroids is less likely to be cost-effective (ICER=£88,333 vs £23,250 in the base case). Similarly, the ICER for a strategy starting with TCF product increased to over £787,000 compared to starting with concurrent treatment (£174,500 in the base case).

M.3.2.5 4-week quantity of TCF product

In the base case, hypothetical patients are assumed to use 134.0 g of TCF product during 4 weeks of treatment. Bottomley and colleagues used a much lower value for this input (92.6 g), and we

explored how the results of the NCGC analysis might change if this lower estimate was used. The cost of 92.6 g of TCF product was £61.27 (compared to £94.26 in the base case). The results of this sensitivity analysis showed that the ICER for TCF product improved compared to the base case (£124,400 vs £174,545); however this is still well above the NICE cost-effectiveness threshold of £20,000 per additional QALY. Initial therapy with twice daily potent corticosteroid or concurrent vitamin D analogue and potent corticosteroid is still more likely to be considered cost-effective.

M.3.2.6 Unit costs of potent corticosteroids and vitamin D analogues

The base case assumed that the cost for each topical was based on the product and formulation with the lowest unit cost per gram/millilitre. Given that clinicians and patients may have preferences for different products or formulations, it was considered necessary to explore how variation in price of topicals, particularly potent corticosteroids and vitamin D, might affect the results. To do this, the highest cost (per gram) potent corticosteroid Synalar gel (fluocinolone acetonide) was assumed in place of Betnovate cream or ointment. The cost of Synalar gel is around four times that of Betnovate cream/ointment. In another analysis, the most costly vitamin D ointment, Curatoderm (tacalcitol), was assumed instead of Silkis (calcitriol). The cost of Curatoderm is around 2.5 times more costly than Silkis and 1.6 times more costly than Dovonex (calcipotriol) ointment. In a final sensitivity analysis, both Synalar gel and Curatoderm were used. Results in terms of incremental cost-effectiveness ratios are presented in Table 23.

Table 23: Incremental cost per QALY gained under different treatment cost assumptions

Strategy	Base Case	Synalar gel	Curatoderm ointment	Synalar gel and Curatoderm ointment
PS BD - Concurrent - Coal Tar BD				
Concurrent - PS BD - Coal tar BD	£23,250	£4,365	£73,192	£51,039
TCF OD - PS BD - Coal Tar BD	£174,545	£160,437	£149,431	£115,158

When the cost of Synalar gel is used, the ICER for starting with concurrent therapy and then moving to potent corticosteroid compared to the reverse, decreases substantially from the base case (£4,365 compared to £23,250), becoming optimal given the NICE threshold. The ICER for this strategy when only the cost of Curatoderm ointment is used and when Synalar gel and Curatoderm ointment, actually increase relative to the base case. Even with increased costs for potent corticosteroid and vitamin D, once daily TCF product is unlikely to be cost-effective compared to concurrent therapy unless the willingness to pay threshold is well over £100,000 per QALY gained.

M.3.2.7 Sensitivity analyses – Restricted comparators

The base case analysis put several conditions on the way topicals could be sequenced (see M.2.1.1). These conditions did not restrict how potent corticosteroids were fit into treatment sequences other than that they could not appear in all three lines of treatment. This included their use as part of concurrent or combined (TCF product) treatment. The GDG expressed concern that these restrictions may not fully reflect the caution they would use in prescribing trials of potent corticosteroids, in that the BNF discourages continuous use of potent corticosteroids for more than 8 weeks at a time. The GDG was also concerned that the analysis did not fully capture the safety risks associated with the continuous or intermittent use of twice daily potent steroids. In a series of sensitivity analyses, various additional restrictions were placed on the treatment sequences.

In the first scenario, it was assumed that interventions that included potent corticosteroids could not be offered consecutively. For example, once daily TCF product could not be offered after treatment with once or twice daily potent corticosteroids, nor could twice daily potent corticosteroid follow once daily potent corticosteroid. Under this assumption, starting with twice daily corticosteroid, then trying twice daily vitamin D analogue and then using both concurrently would represent the best value for NHS resources given a £20,000 per QALY threshold. Starting with concurrent treatment would only be cost-effective at thresholds of greater than £33,000 and TCF product would only be cost-effective at thresholds over £202,000.

In the second scenario, it was assumed that twice daily corticosteroid could not be prescribed as a first or second line topical therapy, but consecutive use of potent corticosteroids was permitted. Under this scenario, the optimal strategy was to start with concurrent corticosteroid and vitamin D analogue, then try twice daily vitamin D analogue alone and finally twice daily potent corticosteroid only. This had an ICER of £18,000 per QALY gained compared to once daily potent corticosteroid followed by concurrent treatment and then twice daily coal tar. Strategies including TCF product either as second or first line were not cost-effective unless the threshold was over £110,000 and £446,000, respectively.

A third scenario combined the first and second scenarios, such that twice daily potent corticosteroid could not be prescribed as first or second line treatment and no sequences could include consecutive lines of potent steroid containing strategies. Under these conditions, the same sequence as in scenario 2 is most cost-effective (Concurrent – vit D BD – PS BD). TCF product replaces twice daily steroid in that sequence only if the threshold willingness to pay is £134,000 and replaces concurrent treatment in the same sequence if the threshold is £202,000.

In a fourth and final scenario, twice daily potent corticosteroid was removed entirely and no potent steroid containing products could be prescribed consecutively. Under this assumption, the most cost-effective sequence was initial concurrent treatment followed by twice daily vitamin D alone and then twice daily coal tar. TCF product replaces twice daily coal tar in that sequence at a threshold of over £47,000 and replaces concurrent treatment at a threshold of over £489,000.

Results from all aforementioned sensitivity analyses (i.e. treatment effects, early versus late response, reduced adherence, cost of potent corticosteroids and vitamin D and so on) were reinterpreted within the context of these restricted comparator scenarios. The conclusions from each scenario presented here were insensitive to changes in the tested parameters. For example, concurrent therapy followed by twice daily vitamin D followed by twice daily potent corticosteroids was optimal across all tested parameter variation under the conditions that twice daily potent corticosteroids could not be offered as initial treatment or when steroids could not be used consecutively. Furthermore, once daily TCF product was consistently more effective but never found to have an ICER below or near to the NICE £20,000 per QALY threshold.

M.3.2.8 Downstream resource use and cost

Changes to the assumed probability of referral to secondary care and proportion offered phototherapy have no meaningful effect on the conclusions of the base case. The probability of referral to secondary care was varied downwards to 40% and upward to 80%. When referral occurred less often than in the base case, there was no change to the rank order of strategies, but the ICER for a strategy where TCF product was used first instead of concurrent treatment increased to £200,000 per additional QALY. When referral occurred more often than in the base case, there was still no change in the rank order, but the ICER for TCF product was slightly lower. If the probability of undergoing UVB phototherapy upon referral was higher than in the base case (50% vs 30%), then the ICER for TCF product compared to concurrent treatment reduced slightly, but not enough to make it cost-effective. Finally, if instead of assuming patients are treated with UVB phototherapy, it is assumed they receive outpatient day care treatment with specialist supervised

topical therapies, then the ICER for concurrent therapy before potent corticosteroids alone increases to over £30,000 per QALY and the ICER for initial TCF product instead of concurrent therapy decreases to £155,000 per QALY.

If the time horizon is extended for 2 to 3 years and cumulatively more patients see a specialist and move on to UVB phototherapy, then initial treatment with concurrent vitamin D and potent corticosteroids becomes more cost-effective than starting with potent corticosteroids alone. When the time horizon is extended, TCF product becomes more cost-effective compared to concurrent treatment (ICER = £118,067 at 2 years; ICER = £90,710 at 3 years; ICER=£75,255 at 5 years; ICER=£73,541 at 10 years), but is still very unlikely to be considered cost effective given the NICE willingness to pay threshold of £20,000 per QALY gained. Visual inspection of the health state membership probabilities over a 10-year time horizon indicates that patients are no longer transitioning between health states after 8 years because they have all reached long-term management with a GP or specialist by this point. This suggests that the ICER for TCF product is unlikely to come down any further even if the model time horizon is extended beyond 10 years.

M.4 Discussion

M.4.1 Summary of results

In assessing the relative cost-effectiveness of alternative topical therapies in patients with mild to moderate psoriasis limited evidence was available from the published economic literature. The evidence that was identified and included in the health economic review had potentially serious limitations and therefore the GDG considered it a priority to undertake original evaluation for the guideline in order to inform recommendations. This analysis showed that there were relatively small differences in terms of benefit between different topical sequences, but the differences in terms of cost were quite substantial. Based on the mean costs and benefits of 118 compared sequences, the analysis suggests that initial treatment with potent corticosteroids followed by concurrent treatment with potent corticosteroid and vitamin D analogue (morning/evening application) and followed then by twice daily coal tar therapy is likely to represent the most cost-effective sequence for implementation in primary care. Uncertainties in the analysis were explored through sensitivity analysis which showed that in some scenarios

- Once daily potent corticosteroid or concurrent treatment should come first in the sequence
- Twice daily vitamin D analogue should come second or third in the sequence, after concurrent treatment
- TCF product should be offered third in the sequence, after potent corticosteroids and concurrent treatment

Sequences starting with once daily TCF product were slightly more effective than the same sequence starting with concurrent potent corticosteroid and vitamin D analogue; however, the very modest additional benefit (0.0011) would only be considered potentially cost-effective if willingness to pay thresholds were between £100,000 and £500,000 per QALY gained.

M.4.2 Limitations & interpretation

The analysis has several limitations which were considered carefully by the GDG. Firstly, the analysis evaluates treatment sequences even though the available trial data compares single topicals head to head without sequencing. In order to apply the treatment effects within the sequencing model, we assumed that treatment effects were independent. That is, we assumed the effectiveness of TCF product as a second or third line topical was equal to its effectiveness as a first line agent and that this was true regardless of other topicals it may follow. The GDG did not believe this to be a significant limitation given that the patients included in the overwhelming majority of RCTs were

reported to have psoriasis for longer than 5 years, during which the can be assumed to have previously tried, succeeded and/or failed various topical treatments.

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

The model was also focused on the induction of disease clearance as opposed to the maintenance of clearance. Trials focusing on maintenance were limited in number and inadequately reported for use in the economic model. In particular, there was uncertainty as to how maintenance treatments were applied in the trials and therefore incorporating such evidence and assumptions into the model was considered too difficult and unlikely to be valid.

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

The model estimated the health gain for each treatment by mapping the change in PASI score to the EQ-5D based on observational evidence. However, it has been noted that several important areas of health-related quality of life for people with psoriasis are not directly assessed by the EQ-5D questionnaire[75]. Therefore it is possible that the EQ-5D may lack content validity for these patients. Research is ongoing in this area. But we note that even using a £30,000 per QALY threshold rather than £20,000 would not change the conclusions of our analyses. Therefore only if the EQ-5D is under-estimating health gain of one treatment compared to another by a considerable extent, could this pose a serious limitation.

The analysis specifically found twice daily potent corticosteroid to be highly cost-effective, but the GDG expressed concern that the well known side effects of potent corticosteroids (e.g. skin atrophy, rapid relapse) were not adequately captured in the economic model owing to a lack of data. Twice daily potent corticosteroids came out more cost-effective than once daily, largely because the quantities of topical used for once and twice daily application were very similar, yet the network meta-analysis showed a non-significant trend toward twice daily being more effective in the investigator assessed outcomes used in the base case (OR=1.807, 95% CrI 0.42 to 8.07). However, this trend is reversed for the patient assessed outcome – twice daily performed less well than once daily (OR=0.714, 95% CrI 0.14 to 3.55). This finding is reflected in the results of this sensitivity analysis where patient reported response was used, which show once daily to be more cost-effective than twice daily. The consensus of the GDG was that they could not be certain that twice daily potent corticosteroids were more effective than once daily potent corticosteroids. They concluded that even if twice daily application was more effective at inducing clearance or near clearance than once daily application, the risks of higher dose steroids were very likely to outweigh the potential benefits and make the intervention comparatively less effective and cost-effective. Therefore the GDG excluded strategies that included twice daily corticosteroids in the first two lines of treatment. It was considered appropriate as third-line treatment, as the number of patients exposed to the risks would be fewer but the need for efficacy more urgent. In order to avoid continuous treatment with steroids for more than 8 weeks the GDG also chose to exclude strategies that contained corticosteroids in two consecutive lines of treatment. After these considerations the most cost-effective strategy was:

- 1st line – Concurrent treatment with potent corticosteroid and vitamin D analogue (morning/evening application)

- 2nd line – twice daily vitamin D analogue
- 3rd line – twice daily potent corticosteroid

The GDG specifically considered whether they should offer concurrent treatment (morning/evening) with two separate topicals or offer combined treatment in a single product for use just once daily. They considered the results of the cost-effectiveness analysis which showed that combined treatment (once daily TCF product) is not cost-effective compared with concurrent treatment. This is because the network meta-analysis found them to have similar efficacy, but TCF product is much more costly (unit cost of 120 g combined product containing calcipotriol monohydrate and betamethasone dipropionate is between 2 and 4 times more costly than combined unit cost of 100 g of vitamin D analogue and potent corticosteroid each). This is true even when the most costly potent corticosteroid and vitamin D products and formulations are assumed to be prescribed. The GDG considered whether a once daily application of the combined product may be cost-effective when considering the problems many patients have adhering to twice daily treatment regimens. The results of a sensitivity analysis wherein 40% of patients prescribed concurrent therapy were assumed to apply only their potent corticosteroid once per day showed that the very small benefits of once daily combined product were still outweighed by its extra cost. The GDG concluded that the combined formulation product as first-line treatment produced enough additional benefit to justify its substantial additional cost.

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

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

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

In thinking about the potential risks of prescribing potent, and in select cases very potent corticosteroids, the GDG considered it essential to build in monitoring to assess efficacy and adverse events. The time horizon of the economic model was too short (1 year) to explicitly consider annual monitoring in the long term; however, it is very likely that the extra cost of an annual GP or specialist visit would be offset by the avoidance of irreversible adverse events that are associated with inappropriate and unsafe use of corticosteroids.

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

M.4.3 Generalisability to other populations / settings

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

M.4.4 Comparisons with published studies

The findings from the NCGC original economic analysis are quite different from the results of the most similar published study by Bottomley and colleagues[62]. Bottomley and colleagues found 8 weeks of once daily TCF product to dominate other modelled strategies including once and twice daily vitamin D analogue followed by potent corticosteroid, potent corticosteroid followed by vitamin D analogue and 8 weeks of concurrent treatment with vitamin D analogue and potent corticosteroid. Although the analysis appears to have been executed well, the estimates of effect and resource use had limitations which called the conclusions of the analysis into question.

The biggest differences in the results of the NCGC analysis presented here and the analysis undertaken by Bottomley has to do with the treatment effect sizes used. In their analysis, concurrent treatment was found to be very ineffective, with just 14.9% of patients responding with a PASI75 compared to TCF product to which 50.3% of patients responded (RR=3.38). The NCGC analysis showed a much small difference between these treatments, with 65.1% of patients responding to concurrent treatment and 70.7% responding to TCF product (RR=1.09).

In addition, the estimate they used for quantity of topical used per 4-week treatment period was 92.6 g, compared to the estimate used in the NCGC analysis 134.0 g. Based on these estimates of resource use, the NCGC analysis assumes 4 weeks of TCF product costs £29.26 more than Bottomley and colleagues did. Furthermore, the difference between TCF product and concurrent treatment is different between the analyses. The additional cost of TCF product was £36.91 in Bottomley and more than twice that, £76.34, in the NCGC analysis. We performed a sensitivity analysis in which we assumed the same quantity of TCF product used by Bottomley and colleagues (i.e. 92.6 g, £61.27). The ICER for TCF product improved compared to the base case (£124,400 vs £174,545), but was still well above the NICE cost-effectiveness threshold of £20,000 per additional QALY.

The one thing that Bottomley and colleagues were able to capture that the NCGC analysis was not had to do with the potential disutilities associated with adverse events; however these inputs were not reported, were not included in their base case and, their impact on the results were not reported in full. The authors simply state that the influence of AEs 'had no impact on the results.'

M.4.5 Conclusion

- New economic analysis from a current UK NHS and PSS perspective comparing 118 different sequences of topical therapies found twice daily potent corticosteroids or concurrent treatment (morning/evening) with potent corticosteroid and vitamin D analogue to be the most cost-effective options for the first and second line treatment of patients with mild to moderate chronic plaque psoriasis. This conclusion was robust to the majority of sensitivity analyses undertaken.
    - The base case and sensitivity analyses showed that the choice of third line treatment in a given sequence was highly uncertain. Depending upon the data used and assumptions made, third line treatment with twice daily coal tar, twice daily vitamin D analogue or once daily TCF product was likely to be most cost effective.

M.4.6 Implications for future research

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

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

N.1 Introduction

The review of clinical evidence for topical therapies used in the treatment of individuals with mild to moderate scalp psoriasis showed that there were several treatment options – tars, corticosteroids (potent and very potent), vitamin D analogues and combination products – each associated with certain advantages and disadvantages. The results of the network meta-analysis indicated that some interventions, such as very potent corticosteroid as well as combined vitamin D analogue and potent corticosteroid, were more likely to induce clearance or near clearance than others. Given that these combined and concurrent application strategies carry additional cost compared to both their individual constituent parts and compared to other topical alternatives, it is important to consider whether these additional costs are justified by additional health benefits in terms of improved quality of life.

One cost-effectiveness analysis was identified in the published literature, but it had methodological limitations that called its conclusions into question. The analysis by Affleck[76] did not include all of the relevant comparators under consideration for the guideline, namely very potent corticosteroids. Furthermore, the treatment effects used in their analysis differed from those found in the NCGC clinical review and network meta-analysis, and this difference was considered likely to affect the conclusion of the analysis.

Due to the limitations of the available economic evidence and the importance of this area in clinical practice, the GDG considered the development of an original cost-effectiveness model to evaluate topical therapies for scalp psoriasis to be a high priority. The decision modelling presented here was developed in close collaboration between the health economist, the rest of the NCGC technical team and GDG members.

N.2 Methods

N.2.1 Model overview

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

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

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

The performance of alternative treatment sequences was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness.

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

N.2.1.1 Comparators

The aim of the analysis was to identify the most cost-effective sequence of first, second and third line topical therapies. It was important to model sequences given that most patients will commence treatment with one topical and then try others before moving on to more intensive treatments such as specialist applied topicals and/or systemic therapy. Table 24 presents the list of possible first, second and third line treatments which may be combined in a sequence.

Table 24: Possible sequences of first, second and third line treatment

First line	Second line	Third line
Vitamin D OD	Vitamin D OD	Combined OD
Vitamin D BD	Vitamin D BD	Very potent corticosteroid OD
Potent corticosteroid OD	Potent corticosteroid OD	Very potent corticosteroid BD
Potent corticosteroid BD	Potent corticosteroid BD	Coal tar polytherapy (Capasal)
Combined OD	Combined OD	Referral to specialist
Very potent corticosteroid OD	Very potent corticosteroid OD	
Very potent corticosteroid BD	Very potent corticosteroid BD	

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

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

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

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

N.2.1.2 Population

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

N.2.1.3 Time horizon, perspective, discount rates used

The analysis took a UK National Health Service and Personal Social Services costing perspective, with costs expressed in 2011 UK sterling. A 1-year time horizon was considered clinically relevant and sufficiently long enough to capture important costs and consequences of first-line treatment in primary care. Since the time horizon was 1 year, no discounting rates were applied to either costs or benefits. Extensions to the time horizon were explored in sensitivity analyses, and for these a 3.5% discounting rate was applied to costs and benefits.

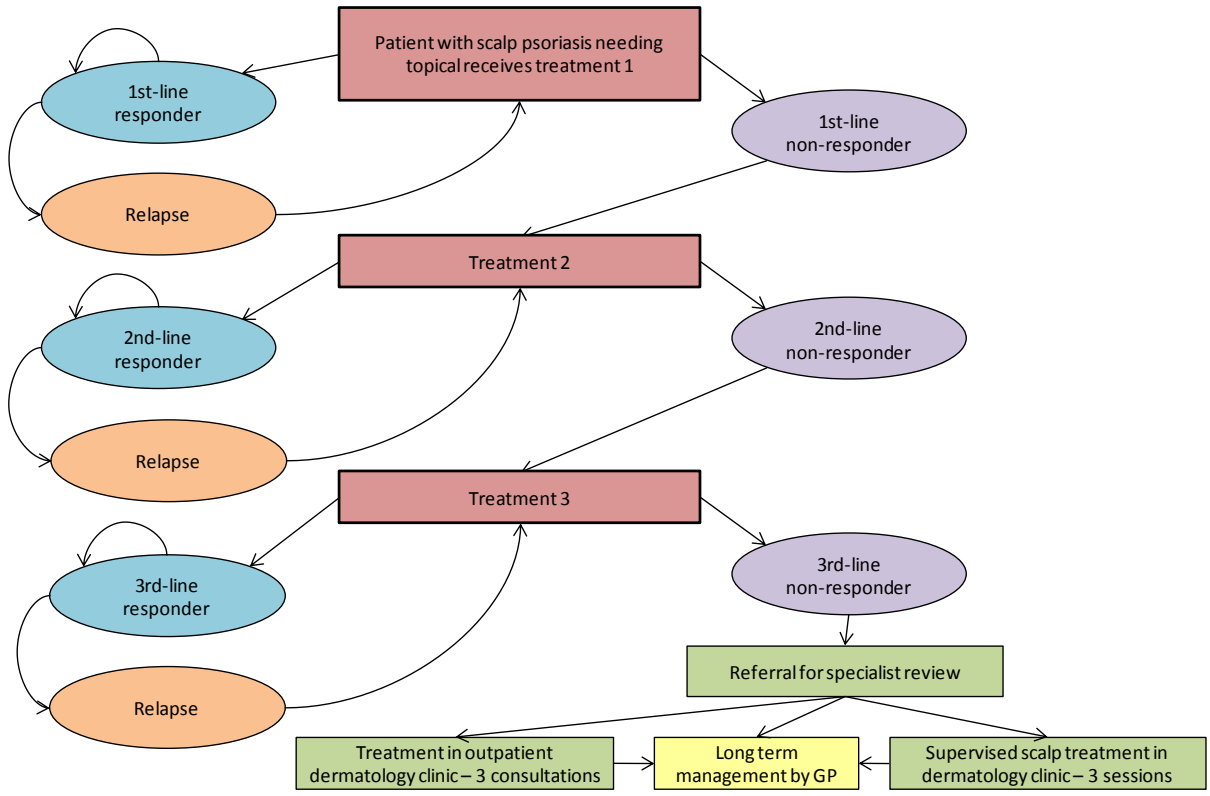
N.2.2 Approach to modelling

N.2.2.1 Model structure

A Markov model was constructed in TreeAge Pro 2009 to capture the different costs and effects associated with a given sequence of topical treatments. It was built to reflect transitions between a set of mutually exclusive health states, defined by response and non-response to treatment. The Markov model and how patients move through the pathway is illustrated in Figure 354. The structure of the model developed by the NCGC was adapted from the model developed by Affleck and colleagues[76] and was validated by the GDG as a reasonable reflection of current clinical practice.

The consequences of a given topical treatment are reflected as a set of possible transitions between health states over a series of discrete time periods, called cycles. In Figure 354, health states are depicted as ovals and interventions are depicted as rectangles. Movement between various health states is governed by transition probabilities, derived from the systematic review of clinical effectiveness data. Thirteen 4-week cycles were modelled, resulting in a 1-year time horizon for the analysis, with a half-cycle correction applied.

Figure 354: Patient flow diagram for the Markov model of topical treatments for scalp psoriasis



The model assumes that all hypothetical patients commence treatment with a given topical and experience one of two outcomes: response (defined as clearance/near clearance of their scalp psoriasis) or no response (defined as something less than clearance/near clearance of their scalp psoriasis). Patients who achieve clearance/near clearance are assumed to stop treatment and either maintain clearance/near clearance in the absence of treatment or they relapse. Patients who relapse are assumed to resume treatment with the same topical and again face a probability of responding or not responding. Patients who fail to achieve clearance on a given topical after 8 weeks (or 4 weeks in the case of very potent corticosteroids) are assumed to return to their GP and receive a prescription for an alternative topical therapy.

Patients can receive up to three different topical therapies before being referred by the GP to a specialist review in an outpatient dermatology clinic where second-line treatment options could be considered. Some proportion of these referred patients will be kept on topical therapies, receive support and advice at the review consultation and be discharged back to their GP for long-term management. Another group of those referred will be treated over 3 appointments in outpatient dermatology and some will undergo supervised scalp treatment with intensive topical therapy over the course of 3 outpatient dermatology appointments. Following referral and management in the specialist setting, they will be managed by their GP with 3-monthly appointments.

N.2.2.5 Uncertainty

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

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

N.2.3 Model inputs

N.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 9 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 25: Summary of base-case model inputs

Input	Data	Source
Comparators	See Table 24	
Population	Individuals with mild to moderate scalp psoriasis	
Perspective	UK NHS and & PSS	NICE reference case[63]
Time horizon	1 year	
Discounting	Not applicable (a)	

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

Table 26: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Source/notes
Baseline Risk (placebo/vehicle BD)			
clear/nearly clear	11.3%	Beta: α= 42; β= 331	95% CI: 8.1% to 14.5% Network meta-analysis (see Appendix L)
Efficacy (Odds ratio compared to Baseline)			
Vitamin D OD	4.168	5,000 simulated odds ratios from the NMA were used	Network meta-analysis (see Appendix L)
Vitamin D BD	4.224		Network meta-analysis (see Appendix L)
Potent corticosteroid OD	10.34		Network meta-analysis (see Appendix L)
Potent corticosteroid BD	7.665		Network meta-analysis (see Appendix L)
Very potent corticosteroid OD	17.76		Network meta-analysis (see Appendix L)
Very potent corticosteroid BD	28.52		Network meta-analysis (see Appendix L)
TCF product OD	14.16		Network meta-analysis (see Appendix L)
Coal tar polytherapy	1.839		Network meta-analysis (see Appendix L)

Parameter description	Point estimate	Probability distribution	Source/notes
Relapse			
All topical therapies	35.5%	Beta: α=192; β= 137	Assumption; test range in sensitivity analysis
Probability of specialist referral and subsequent management			
Referral for specialist review	100%		Assumption
Specialist topicals advice and management by GP	50%		Assumption
Topicals with specialist advice and follow-up	25%		Assumption
Intensive scalp treatment in outpatient day care	25%		Assumption
Probability of response to Intensive scalp treatment	75%		Assumption
Health-related Quality of Life (a)			
Response – Clear/nearly clear	0.7962	See Table 30	Affleck 2011[76]
Non-response – Not clear/nearly clear	0.7781	See Table 30	Affleck 2011[76]
Baseline	0.7670	See Table 30	Affleck 2011[76]
Resource use			
4 weeks of topical treatment			
Vehicle BD	77.6 g	Gamma: α=25.23 β=3.08	Data only available for once daily from Jemec 2008[50], Jemec 2011[77], Tyring 2010[54]
Vitamin D OD	89.2 g	Gamma: α=238.64 β=0.37	Jemec 2008[50], Jemec 2011[77], van de Kerkhof 2009[55]
Vitamin D BD	85.6 g	Gamma: α=38.06 β=2.25	Affleck 2011[76]
Potent corticosteroid OD	87.35 g	Gamma: α=173.49 β=0.50	Buckley 2008[46], Jemec 2008[50], Jemec 2011[77], van de Kerkhof 2009[55]
Potent corticosteroid BD	90.16 g	Gamma: α=184.82 β=0.49	
Very potent corticosteroid OD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
Very potent corticosteroid BD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
Combined vitamin D and potent corticosteroid OD	71.4 g	Gamma: α=127.25 β=0.56	Buckley 2008[46], Jemec 2008[50], Jemec 2011[77], Tyring 2010[54], van de Kerkhof 2009[55]
Coal tar polytherapy	250 mL	Gamma: α=25.00 β=10.00	assumption
Health care consultations			

Parameter description	Point estimate	Probability distribution	Source/notes
GP consultations following non-response to topical treatment	1 per treatment change		Assumption
Specialist outpatient consultation	1 following failure of 3 topicals		Assumption
Specialist follow-up and support	3 additional outpatient visits		Assumption
Intensive scalp treatment in outpatient day care	3 visits (at 1, 3 and 6 months)		Assumption
Long term management by GP	1 visit per 3 months		Assumption
Cost (£)			
Unit cost of topical treatment			
Vehicle	500g = £5.83		Doublebase gel
Vitamin D	60 g = £12.70; 120 g = £26.07		Calcipotriol scalp solution
Potent corticosteroid	100 g = £3.75		Betacap scalp application 60g Synalar (Fluocinolone acetonide) gel = £10.02 30 g Synalar gel = £5.56
Very potent corticosteroid	100 g = £10.42; 30 g = £3.07		Dermovate scalp application
Combined vitamin D and potent corticosteroid	60 g = £36.50; 120 g = £67.79		Dovobet gel
Coal Tar	250 g = £4.69		Capasal shampoo
Unit cost of healthcare consultations			
GP consultation	£28		PSSRU 2010[69]
Specialist outpatient consultation	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[70]
Specialist outpatient nurse consultation (first visit)	£81	lognormal: log of mean = 4.40 se of logs = 0.03	NHS Reference costs 2009-10[70]

Parameter description	Point estimate	Probability distribution	Source/notes
Specialist outpatient nurse consultation (follow-up visit)	£64	lognormal: log of mean = 4.15 se of logs = 0.05	NHS Reference costs 2009-10[70]
Intensive scalp treatment (JD02C)	£351	lognormal: log of mean = 5.86 se of logs = 0.05	NHS Reference costs 2009-10[70]

(a) See section N.2.3.6 for more details on how utilities were parameterised in the model

N.2.3.2 Baseline event rates

Creams and emollients with no active ingredient are a typical first-line therapy for patients presenting with scalp psoriasis. Although the primary objective of this model is to identify cost-effective sequences of topical therapies with active ingredients, it is useful to compare all strategies to a baseline probability of achieving clearance with a topical without an active ingredient. The absolute probability of achieving clearance or near clearance with twice daily vehicle/placebo was calculated by aggregating the number of people achieving clear/nearly clear across the twice daily vehicle/placebo arms of randomised controlled trials included in the systematic review of topical scalp therapies and dividing by the aggregate sample size from the same arms. This resulted in a probability of 11.3% (95% CI: 8.1% to 14.5%) for achieving clear/nearly clear. For the probabilistic analysis, uncertainty in the risk parameter for vehicle/placebo was incorporated using a beta distribution (α=42; β=331).

N.2.3.3 Relative treatment effects

In order to estimate the effectiveness for all other comparators in the model, the treatment effect estimates from the network meta-analysis of scalp treatment (see Appendix L) were applied to the baseline probabilities outlined above. The only estimates available and therefore used relate to the investigator assessed outcome (IAGI/PGA). The odds ratios used in the analysis are presented in Table 27.

Table 27: Relative treatment effects from NMA

Intervention	Odds ratio (95% CI) vs placebo
Vitamin D OD	4.168 (.69 to 22.63)
Vitamin D BD	4.224 (1.36 to 15.94)
Potent corticosteroid OD	10.34 (1.75 to 56.48)
Potent corticosteroid BD	7.665 (2.62 to 23.92)
Very potent corticosteroid OD	17.76 (4.00 to 113.8)
Very potent corticosteroid BD	28.52 (13.6 to 68.09)
Combined vitamin D and potent corticosteroid OD	14.16 (2.84 to 67.34)
Coal tar polytherapy	1.839 (0.39 to 11.61)

To calculate the absolute probability of response to a given topical treatment (presented in Table 12), the odds ratios of that intervention compared to twice daily placebo from the network meta-analysis was converted into a relative risk and applied to the 11.3% baseline risk (e.g. probability of response to twice daily placebo) using the following formula:

$$P_T = P_0 \times RR$$

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

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

Where: OR is the odds ratio of the treatment compared to P_0, the baseline probability.

For the probabilistic implementation of the analysis, uncertainty in the comparative treatment effects is incorporated by using 5,000 of the simulated odds ratios from the network meta-analysis. Using the simulated outputs allows us to preserve the joint posterior distribution from the network meta-analysis and any correlation of treatment effects.

Table 28: Probability of response

Intervention	Probabilities of response
Vehicle BD	11.26%
Vitamin D OD	34.59%
Vitamin D BD	34.89%
Potent corticosteroid OD	56.75%
Potent corticosteroid BD	49.31%
Very potent corticosteroid OD	69.26%
Very potent corticosteroid BD	78.35%
TCF OD	64.24%
Coal Tar polytherapy	18.92%

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

Early vs late response

The data used to estimate the overall probabilities of response to treatment (Table 12) were based on trials of varying duration, 2 to 12 weeks follow-up. In the clinical review, we looked for evidence that would suggest when the appropriate time to assess response to treatment was. Where trials were of longer duration (i.e. 8 to 12 weeks) the evidence suggested that patients were still improving between 4 and 8 weeks. On that basis the GDG felt it would be inappropriate to assume that a) everyone who will respond will do so within 4 weeks and that b) patients who were not clear/nearly clear at the end of week 4 should discontinue treatment and be classified as a non-responders. Therefore, the model assumes that patients will be treated with a given topical for up to 8 weeks. If they respond in the first 4 weeks, then they are assumed to discontinue treatment. If they have not yet responded, then they are assumed to carry on for a further 4 weeks after which they discontinue having responded or not responded. This applies to all topicals except for very potent corticosteroids, which for reasons of safety are assumed to be trialled for a maximum of 4 weeks.

On that basis, where data from trials with longer follow-up was available, we looked to estimate what proportion of patients who responded by the end of follow-up had done so within the first 4 weeks or the last 4 weeks. The data with which to estimate this was only available from three studies[50,51,55]. These studies reported response rates at 4 weeks and 8 weeks for vehicle, potent corticosteroid, vitamin D analogue and two-compound formulation product.

The data showed that more than half of all responders at 8 weeks had responded fully by 4 weeks across all topicals, including vehicle alone. The data from the three trials was broadly similar for each

topical and therefore the probabilities of response at 4 weeks versus 8 weeks were estimated by calculating a weighted average across the studies.

The weighted average proportion of early (0 to 4 weeks) and late (5 to 8 weeks) responders from the studies were applied to the overall response figures generated from the network meta-analysis in order to estimate the probabilities of response in the first 4 weeks of treatment and the second 4 weeks of treatment (presented in Table 13). In the absence of data, the assumption was made that the proportions of early and late responders is the same for once and twice daily application of a given topical. In other words, this assumes that twice daily application of a topical does not induce response earlier than once daily application of the same topical. This assumption was validated by GDG member experience, which was that frequency of application did not have a demonstrable effect on speed of response.

Table 29: Probabilities of response: overall, early and late

Intervention	Overall probability of achieving response	Of all responders, proportion who will respond in first 4 weeks	Probability of early response (0 to 4 wks)	Probability of late response (5 to 8 wks)
Vehicle	11.26%	65%	7.3%	4.31%
Vitamin D OD	34.59%	61%	21.2%	17.03%
Vitamin D BD	34.89%	61%	21.4%	17.22%
Potent corticosteroid OD	56.75%	85%	48.0%	16.85%
Potent corticosteroid BD	49.31%	85%	41.7%	13.06%
Very potent corticosteroid OD	69.3%	100%	69.3%	NA
Very potent corticosteroid BD	78.3%	100%	78.3%	NA
TCF OD	64.24%	87%	55.6%	19.46%
Coal Tar polytherapy OD	18.92%	50%	9.5%	10.45%

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

N.2.3.4 Relapse

Psoriasis is a relapsing and remitting chronic condition and achievement of clearance/near clearance with active treatment has no long-term effect on the natural history of chronic plaque psoriasis affecting the scalp. As in the analysis for topicals used in all sites, the RCT data with regard to relapse was sparse for the same reasons: variable trial follow-up and differences in the definition of relapse. For the economic model, the GDG defined relapse as any deterioration to the point at which retreatment is required.

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

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

N.2.3.5 Referral and specialist management

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

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

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

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

N.2.3.6 Utilities

Achievement of clearance or near clearance and associated utility gain was used in the model to determine the impact of scalp psoriasis treatment on overall health. Estimates of utility gain were taken from a recent cost-utility analysis included in the health economic review[76]. The mean utility at baseline was 0.767 and mean utility gain associated with clearance/near clearance was 0.0292. It is expected that patients who do not achieve clearance or near clearance will still experience some level of improvement on treatment; therefore, these patients also experience a modest utility gain of 0.0111. It is assumed that patients who fail to respond and ultimately reach the point of requiring referral to a specialist return to their baseline level of utility (0.767).

Table 30: Health state utility values

Health State	Health state utility	Utility loss compared to above health state	Probability distribution for mean utility loss (a)	Source of health state utility/Notes
Full health	1.00			Theoretical anchor state
Response: clear/nearly clear	0.7962	0.2038	Gamma: mean = 0.2038 sd = 0.0407	Affleck 2011[76]
Non-response: Not clear/nearly clear	0.7781	0.0181	Gamma: mean = 0.0181 sd = 0.0036	Affleck 2011[76]
Baseline	0.7670	0.0111	Gamma: mean = 0.0111 sd = 0.0022	Affleck 2011[76]

(b) Utility losses were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically (i.e. such that response was always greater than non-response, which was always greater than baseline). No error estimates were available from the literature, so it was assumed that the standard deviation (SD) of the mean was 20% of the mean difference between health states.

Key assumptions about utilities in the model:

- Patients who do not achieve clearance at 4 weeks and continue on for a further 4 weeks of topical therapy will improve somewhat and therefore accrue the gain associated with non-responders.
- Patients who relapse following clearance lose the incremental gain between response and non-response (0.0181) before resuming treatment.
- Patients who fail to respond and ultimately reach the point of requiring referral to a specialist or phototherapy return to their baseline level of utility (0.767).
- Patients managed long-term by either a GP or a specialist accrue the gain associated with non-responders.

N.2.3.7 Resource use and cost

Topical therapy

Resource use of alternative scalp treatments was based on reported mean quantities of study drugs used by patients in the RCTs[46,50,54,55,57,77] at the end of trial treatment periods. Mean quantities and distribution parameters for the probabilistic analysis are presented in Table 31.

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

No estimates were available to inform the mean usage of twice daily vitamin D analogue. In the cost-utility analysis by Affleck and colleagues[76], they estimated 4-week mean usage for this strategy to be 85.57 g (95% CI: 58.94-112.2) based on an unpublished trial held on file. We have taken this estimate for use in our model.

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

Unit costs of topicals (Table 32) were taken from the most recent BNF[72]. Given that the interventions were modelled assuming a class effect, the cost of topical had to be selected from a variety of compounds, formulations and package sizes. For simplicity, we used the cost for the scalp formulation of each topical with the lowest unit cost per gram/millilitre.

Table 31: Mean quantities of topicals used per 4-week cycle

Topical therapy	Mean quantity used	Probability distribution	Source/notes
Vehicle BD	77.6 g	Gamma: α=25.23 β=3.08	Data only available for once daily from Jemec 2008[50], Jemec 2011[77], Tyring 2010[54]

Topical therapy	Mean quantity used	Probability distribution	Source/notes
Vitamin D OD	89.2 g	Gamma: α=238.64 β=0.37	Jemec 2008[50], Jemec 2011[77], van de Kerkhof 2009[55]
Vitamin D BD	85.6 g	Gamma: α=38.06 β=2.25	Affleck 2011[76]
Potent corticosteroid OD	87.35 g	Gamma: α=173.49 β=0.50	Buckley 2008[46], Jemec 2008[50], Jemec 2011[77], van de Kerkhof 2009[55]
Potent corticosteroid BD	90.16 g	Gamma: α=184.82 β=0.49	
Very potent corticosteroid OD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
Very potent corticosteroid BD	60 g	Gamma: α=25.00 β=2.40	max suitable quantity for application to scalp according to BNF
TCF OD	71.4 g	Gamma: α=127.25 β=0.56	Buckley 2008[46], Jemec 2008[50], Jemec 2011[77], Tyring 2010[54], van de Kerkhof 2009[55]
Coal tar polytherapy	250 mL	Gamma: α=25.00 β=10.00	Assumption

Table 32: Unit costs of topical therapies for scalp psoriasis

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

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

To calculate the per cycle cost of each topical, the mean quantities were converted into the cheapest combination of the number of packs of topical needed. For example, the mean 4-week dosage for once daily TCF product was 71.4 g. The cheapest combination of packs needed to provide this quantity was one 120 g pack. The 4-week costs of topical treatments based on the mean quantities used are presented in Table 33.

During probabilistic implementation, dosages were drawn from topical specific gamma distributions fitted using the mean of the means reported in the RCTs and its standard error. No mean or standard error was available for very potent corticosteroids or coal tar polytherapy, so the standard error was assumed to be 20% of the assumed mean. The model was built to ensure that the

cheapest combination of packs, as outlined in the example above, could be calculated automatically for any sampled value. For example, if the sample value for once daily TCF product was 47 g, then the cheapest combination would be automatically be calculated as one 60 g pack. Similarly, if the sampled value was 153 g, then the cheapest combination would be one 120 g pack and one 60 g pack.

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

Table 33: Mean cost of 4-week topical treatment

Topical strategy	4-week cost
Vehicle	£0.90
Vitamin D OD	£25.40
Vitamin D BD	£25.40
Potent corticosteroid OD	£3.75
Potent corticosteroid BD	£3.75
Very potent corticosteroid OD	£6.14
Very potent corticosteroid BD	£6.14
TCF product OD	£67.79
Coal Tar polytherapy	£4.69

Health care consultations

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

All patients who fail to respond to a third topical treatment are referred by their GP for specialist review. During the time spent between being referred and the specialist review, patients are assumed to maintain topical treatment, for which the average 4-week cost across all topical treatments was used (£17.88).

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

Table 34: Unit cost of health care consultations

Type of healthcare consultation	Health care resource use	Unit cost per consultation	Probability distribution	Source/notes
GP consultations following non-	• 1 per treatment change	£28		PSSRU 2010[69]

Type of healthcare consultation	Health care resource use	Unit cost per consultation	Probability distribution	Source/notes
response to topical treatment	• 1 visit per 3 months for long term management			
Specialist outpatient consultation (consultant)	• 1 following failure of 3 topicals	£112	lognormal: log of mean = 4.72; se of logs = 0.02	NHS Reference costs 2009-10[70]
Specialist follow-up and support (specialist nurse)	• 3 additional outpatient visits	£64	lognormal: log of mean = 4.15 se of logs = 0.05	NHS Reference costs 2009-10[70]
Intensive scalp treatment in outpatient day care	• 3 visits (at 1, 3 and 6 months)	£351	lognormal: log of mean = 5.86 se of logs = 0.05	NHS Reference costs 2009-10 (JD02C)[70]

N.2.4 Computations

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N.2.5 Sensitivity analyses

A series of one-way sensitivity analyses and scenario analyses were performed to assess how changes in one or more parameters or assumptions might change the conclusions of the analysis. In the first sensitivity analysis, the quantity of TCF product used over a 4 week treatment period was reduced to match the estimate used by Affleck and colleagues[76]. Also, alternative assumptions about the comparators were used to explore what might be appropriate if there were concerns about safety or contraindications.

N.2.6 Model validation

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

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

N.3 Results

N.3.1 Base case

This analysis found that, given a NICE willingness-to-pay threshold of £20,000 per QALY gained, the most effective and cost-effective strategy is likely to be one of starting with once daily very potent corticosteroid and then escalating to twice daily very potent corticosteroid and then trying once daily TCF product if very potent steroids alone are insufficient to induce clearance or near clearance. This conclusion was based on the comparison of mean costs and mean QALYs across 169 modelled sequences. Base case results for non-dominated and non-extendedly dominated strategies are presented in Table 35.

This sequence, starting with very potent corticosteroids once and then twice daily followed by TCF product was expected to generate 0.0014 more QALYs for an additional cost of £26.80 compared to the least costly sequence (once daily potent corticosteroid followed by once and then twice daily very potent corticosteroids). This gives and ICER of £19,143 per QALY gained, which is just under the NICE cost-effectiveness threshold. Based on total net monetary benefits and probabilities of being most cost-effective, there is little difference between the two strategies.

Table 35: Incremental analysis of base case results – scalp psoriasis

Strategy (a)	Cost	Incrmntl Cost	Benefit (QALYs)	Incrmntl benefit (QALYs)	Incremental cost effectiveness ratio (ICER) (£/QALY)	NMB at £20k threshold	Probability most cost effective at £20k threshold
PS OD - VPS OD - VPS BD	£163		0.774			£15,317	27%
VPS OD - VPS BD - TCF OD	£190	£26.80	0.775	0.0014	£19,143	£15,318	28%

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

Mean costs and QALYs and their respective 95% confidence intervals for all 169 strategies, ranked in order of mean net benefits at £20,000 per QALY threshold, are presented in Table 36. These show that the most effective (and cost-effective) strategies involved use of potent and very potent corticosteroids in at least two lines of treatment. Results also showed that a strategy of using vehicle gel or emollient with no active agent only was the most costly and least effective strategy, largely driven by the cost of referrals and specialist management for non-responders. Similarly, a strategy of prescribing coal tar polytherapy for ongoing management was only slightly more effective than continued use of vehicle gel and cost the third most of any treatment sequence. Compared to strategies relying heavily on corticosteroids, strategies that included once or twice daily vitamin D analogue were unlikely to be cost-effective regardless of where they came in a treatment sequence. This finding is driven by their relatively low rank in terms of effectiveness and their relatively high acquisition cost relative to potent and very potent corticosteroids. Two compound formulation product, although third most effective in the network meta-analysis, was found to be cost-effective only as a third line intervention following very potent corticosteroids. Like vitamin D analogues, its high unit cost compared to other cheaper and effective topicals makes it unlikely to represent reasonable value for NHS resources.

A breakdown of total costs by type of resource use (i.e. topicals, GP visits, outpatient consultations, day centre treatments) is presented for all modelled strategies in table 14. Note that these estimates have been derived from a *deterministic* implementation of the base case analysis; therefore, the total costs should be similar, but may not exactly match the mean total costs presented in Table 36, which are *probabilistic*. Disaggregation of costs allows one to observe what part of a given strategy is driving the majority of total cost. Strategies that are less effective tend to have higher downstream costs driven by visits to the GP and referrals for specialist review and/or intensive scalp treatment. Strategies that are very effective are likely to have lower downstream costs, but potentially higher drug costs.

Based on this disaggregation, it becomes clear that strategies with TCF product have relatively high topical costs, some of which are offset by reduced downstream costs in terms of consultations with specialists and intensive treatment in a day care centre setting. The earlier that TCF product appears in the treatment sequence, the greater the proportion of total costs can be attributed to the topical

itself. Strategies with potent and very potent corticosteroids show similar downstream costs as strategies involving TCF product, but because their acquisition cost is dramatically lower (less than one-tenth of the 4-week cost), the overall total cost is significantly lower.

The probabilistic analysis indicates that there is a great deal of uncertainty as to which sequence is optimal (i.e. most cost-effective). No single sequence was most cost-effective at a £20,000 per QALY willingness to pay threshold in more than 30% of simulations; however, looking across strategies indicates that those starting with once daily potent corticosteroid were optimal in 43% of simulations. In 33% of all simulations, following once daily potent with once or twice daily very potent corticosteroid was optimal. In another 44% of simulations, a sequence starting with either once or twice daily very potent corticosteroid was likely to be most cost-effective. The remaining 13% of simulations indicated that twice daily potent corticosteroid was an optimal first line strategy. These trends can also be seen by looking at the rank order of strategies in Table 36, which shows that those starting with potent and very potent corticosteroids have the highest mean net benefits. These statistics indicate that we can be reasonably confident that starting with once daily potent or very potent corticosteroid is going to bring the greatest benefit for resources used, and that escalating to a twice daily very potent corticosteroid is likely to provide further benefit at reasonable extra cost.

Table 36: Mean total costs and QALYs for all modelled comparators

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @ £20k (£)	Probability optimal @ £20k
VPS OD - VPS BD - TCF OD	190	58 to 378	0.775	0.759 to 0.791	15318	28%
PS OD - VPS OD - VPS BD	163	45 to 327	0.774	0.757 to 0.79	15318	27%
VPS OD - VPS BD - Vit D OD	193	59 to 370	0.775	0.758 to 0.79	15305	2%
VPS OD - VPS BD - Vit D BD	194	61 to 366	0.775	0.758 to 0.79	15304	6%
VPS OD - VPS BD - Coal tar polytherapy	194	62 to 357	0.775	0.758 to 0.79	15300	4%
PS BD - VPS OD - VPS BD	177	66 to 330	0.774	0.757 to 0.789	15295	11%
PS OD - PS BD - VPS BD	179	60 to 330	0.773	0.756 to 0.789	15285	9%
PS OD - VPS BD - TCF OD	205	61 to 399	0.774	0.757 to 0.79	15274	4%
VPS OD - Vit D OD - VPS BD	221	72 to 396	0.774	0.757 to 0.79	15266	0%
VPS OD - Vit D BD - VPS BD	221	74 to 391	0.774	0.757 to 0.79	15266	0%
PS OD - VPS BD - Vit D BD	208	67 to 376	0.773	0.756 to 0.789	15261	0%
PS OD - VPS BD - Vit D OD	209	62 to 393	0.773	0.756 to 0.789	15259	1%
PS OD - VPS BD - Coal tar polytherapy	209	69 to 374	0.773	0.756 to 0.789	15255	0%
VPS OD - VPS BD - Referral	236	80 to 414	0.774	0.758 to 0.79	15254	0%
PS BD - VPS BD - TCF OD	223	96 to 394	0.773	0.757 to 0.789	15247	1%
VPS OD - TCF OD - VPS BD	261	88 to 449	0.775	0.758 to 0.791	15239	0%
VPS BD - Vit D BD - TCF OD	266	121 to 450	0.775	0.759 to 0.79	15232	1%
VPS BD - Vit D OD - TCF OD	266	115 to 464	0.775	0.759 to 0.79	15232	1%
PS BD - VPS BD - Vit D OD	228	99 to 387	0.773	0.756 to 0.789	15229	0%
PS BD - VPS BD - Vit D BD	229	100 to 382	0.773	0.756 to 0.789	15228	1%
VPS BD - TCF OD - Vit D BD	278	134 to 460	0.775	0.759 to 0.79	15225	0%
PS OD - PS BD - VPS OD	227	52 to 476	0.773	0.754 to 0.789	15225	1%
PS BD - VPS BD - Coal tar polytherapy	231	102 to 379	0.773	0.755 to 0.789	15221	1%

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @ £20k (£)	Probability optimal @ £20k
VPS BD - TCF OD - Coal tar polytherapy	278	136 to 455	0.775	0.759 to 0.79	15221	0%
PS OD - Vit D BD - VPS BD	240	85 to 403	0.773	0.755 to 0.789	15217	0%
PS OD - Vit D OD - VPS BD	241	78 to 419	0.773	0.755 to 0.789	15216	0%
Vit D OD - VPS OD - VPS BD	244	132 to 402	0.773	0.756 to 0.789	15214	0%
Vit D BD - VPS OD - VPS BD	244	133 to 396	0.773	0.756 to 0.789	15213	0%
VPS BD - Vit D OD - Vit D BD	272	123 to 444	0.774	0.758 to 0.79	15212	0%
VPS BD - Vit D OD - Coal tar polytherapy	274	125 to 441	0.774	0.757 to 0.79	15205	0%
VPS BD - Vit D BD - Coal tar polytherapy	276	128 to 436	0.774	0.757 to 0.79	15202	2%
PS OD - VPS BD - Referral	257	94 to 434	0.773	0.755 to 0.789	15202	0%
PS OD - VPS OD - TCF OD	271	52 to 616	0.773	0.755 to 0.789	15194	1%
Vit D BD - PS OD - VPS BD	250	136 to 396	0.772	0.754 to 0.788	15190	0%
Vit D OD - PS OD - VPS BD	252	134 to 412	0.772	0.754 to 0.788	15189	0%
PS OD - TCF OD - VPS BD	285	102 to 470	0.774	0.756 to 0.789	15185	0%
PS BD - Vit D OD - VPS BD	262	129 to 410	0.772	0.754 to 0.788	15182	0%
PS BD - Vit D BD - VPS BD	264	133 to 407	0.772	0.754 to 0.788	15180	0%
PS OD - VPS OD - Vit D BD	273	56 to 567	0.773	0.754 to 0.789	15178	0%
PS OD - VPS OD - Vit D OD	275	52 to 581	0.773	0.754 to 0.789	15175	0%
PS OD - VPS OD - Coal tar polytherapy	273	57 to 552	0.772	0.754 to 0.789	15172	0%
VPS BD - TCF OD - Referral	322	158 to 521	0.775	0.758 to 0.79	15172	0%
TCF OD - VPS OD - VPS BD	318	243 to 445	0.775	0.758 to 0.79	15172	0%
Vit D OD - PS BD - VPS BD	266	155 to 405	0.772	0.754 to 0.788	15170	0%
PS BD - VPS OD - TCF OD	288	80 to 581	0.773	0.755 to 0.789	15168	0%
Vit D BD - PS BD - VPS BD	268	159 to 401	0.772	0.754 to 0.788	15167	0%
PS BD - VPS BD - Referral	285	139 to 443	0.772	0.755 to 0.788	15161	0%
Vit D BD - VPS BD - TCF OD	297	170 to 466	0.773	0.756 to 0.789	15158	0%
PS BD - TCF OD - VPS BD	311	171 to 457	0.773	0.756 to 0.789	15149	0%
PS OD - Vit D BD - VPS OD	295	77 to 575	0.772	0.754 to 0.789	15147	0%
PS BD - VPS OD - Vit D OD	293	81 to 552	0.772	0.754 to 0.789	15146	0%
PS BD - VPS OD - Vit D BD	294	82 to 548	0.772	0.754 to 0.789	15145	0%
PS OD - Vit D OD - VPS OD	297	72 to 590	0.772	0.754 to 0.789	15145	0%
TCF OD - PS BD - VPS BD	331	254 to 445	0.774	0.757 to 0.789	15143	0%
PS OD - PS BD - TCF OD	303	72 to 605	0.772	0.754 to 0.789	15143	0%
VPS BD - Vit D OD - Referral	331	164 to 508	0.774	0.757 to 0.789	15141	0%
PS BD - VPS OD - Coal Tar polytherapy	295	83 to 533	0.772	0.753 to 0.788	15139	0%
VPS BD - Vit D BD - Referral	333	172 to 497	0.774	0.757 to 0.789	15138	0%
PS OD - TCF OD - VPS OD	330	99 to 638	0.773	0.755 to 0.789	15129	0%
Vit D BD - VPS BD - Coal tar polytherapy	307	177 to 450	0.772	0.754 to 0.788	15128	0%

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @ £20k (£)	Probability optimal @ £20k
TCF OD - VPS BD - Vit D BD	358	264 to 491	0.774	0.757 to 0.79	15122	0%
Vit D BD - PS OD - VPS OD	306	128 to 567	0.771	0.753 to 0.788	15120	0%
PS OD - PS BD - Vit D BD	309	80 to 559	0.771	0.753 to 0.789	15120	0%
VPS OD - Vit D BD - TCF OD	349	87 to 671	0.773	0.755 to 0.79	15120	0%
VPS OD - Vit D OD - TCF OD	350	82 to 690	0.773	0.755 to 0.79	15118	0%
Vit D OD - PS OD - VPS OD	308	126 to 580	0.771	0.753 to 0.788	15118	0%
TCF OD - VPS BD - Coal tar polytherapy	359	264 to 486	0.774	0.757 to 0.789	15118	0%
PS OD - PS BD - Vit D OD	311	73 to 576	0.771	0.752 to 0.789	15117	0%
VPS OD - TCF OD - Vit D BD	360	97 to 679	0.774	0.756 to 0.79	15113	0%
PS OD - PS BD - Coal Tar polytherapy	312	82 to 547	0.771	0.752 to 0.788	15111	0%
PS BD - Vit D OD - VPS OD	319	119 to 560	0.771	0.753 to 0.788	15111	0%
PS OD - VPS OD - Referral	329	74 to 610	0.772	0.753 to 0.789	15110	0%
PS BD - Vit D BD - VPS OD	319	119 to 556	0.771	0.753 to 0.788	15110	0%
VPS OD - TCF OD - Coal tar polytherapy	360	97 to 663	0.773	0.755 to 0.79	15108	0%
PS OD - Vit D BD - PS BD	325	93 to 566	0.771	0.752 to 0.788	15102	0%
PS OD - TCF OD - PS BD	348	105 to 626	0.772	0.754 to 0.789	15101	0%
Vit D OD - PS BD - VPS OD	323	143 to 553	0.771	0.753 to 0.788	15100	0%
PS OD - Vit D OD - PS BD	327	88 to 583	0.771	0.752 to 0.788	15100	0%
Vit D BD - PS BD - VPS OD	324	146 to 549	0.771	0.753 to 0.788	15098	0%
VPS OD - Vit D OD - Vit D BD	355	86 to 643	0.773	0.754 to 0.789	15095	0%
PS BD - TCF OD - VPS OD	356	166 to 603	0.772	0.755 to 0.789	15094	0%
Vit D OD - Vit D BD - VPS BD	340	207 to 482	0.771	0.753 to 0.788	15088	0%
VPS OD - Vit D OD - Coal Tar polytherapy	356	87 to 626	0.772	0.753 to 0.789	15088	0%
TCF OD - PS BD - VPS OD	376	255 to 587	0.773	0.756 to 0.789	15088	0%
VPS OD - Vit D BD - Coal Tar polytherapy	357	91 to 616	0.772	0.753 to 0.789	15086	0%
TCF OD - Vit D BD - VPS BD	387	283 to 516	0.773	0.756 to 0.789	15081	0%
Vit D BD - PS OD - PS BD	336	146 to 558	0.771	0.752 to 0.788	15075	0%
Vit D OD - PS OD - PS BD	338	141 to 574	0.771	0.752 to 0.788	15073	0%
PS BD - VPS OD - Referral	355	113 to 591	0.771	0.753 to 0.788	15071	0%
TCF OD - VPS BD - Referral	402	285 to 548	0.774	0.756 to 0.789	15069	0%
Vit D BD - VPS OD - TCF OD	372	148 to 674	0.772	0.754 to 0.789	15067	0%
Vit D OD - VPS OD - TCF OD	373	144 to 694	0.772	0.754 to 0.789	15066	0%
Vit D OD - VPS BD - TCF OD	373	145 to 694	0.772	0.754 to 0.789	15066	0%
Vit D BD - VPS BD - Referral	364	223 to 512	0.771	0.754 to 0.788	15064	0%
Vit D OD - TCF OD - VPS BD	392	237 to 544	0.772	0.755 to 0.788	15054	0%
PS OD - Vit D BD - TCF OD	383	98 to 711	0.772	0.753 to 0.789	15053	0%
Vit D BD - TCF OD - VPS BD	394	259 to 533	0.772	0.755 to 0.788	15052	0%

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @ £20k (£)	Probability optimal @ £20k
VPS OD - TCF OD - Referral	412	114 to 724	0.773	0.755 to 0.79	15051	0%
PS OD - Vit D OD - TCF OD	387	88 to 748	0.772	0.752 to 0.789	15048	0%
TCF OD - VPS OD - Vit D BD	418	258 to 669	0.773	0.755 to 0.789	15045	0%
PS OD - TCF OD - Vit D BD	397	110 to 718	0.772	0.753 to 0.789	15045	0%
Vit D OD - VPS OD - Vit D BD	378	148 to 647	0.771	0.752 to 0.788	15043	0%
Vit D OD - VPS BD - Vit D BD	378	149 to 647	0.771	0.752 to 0.788	15043	0%
TCF OD - VPS OD - Coal tar polytherapy	418	259 to 654	0.773	0.755 to 0.789	15041	0%
PS OD - TCF OD - Coal Tar polytherapy	398	111 to 711	0.772	0.753 to 0.789	15038	0%
PS OD - PS BD - Referral	377	126 to 598	0.771	0.751 to 0.788	15038	0%
Vit D OD - VPS OD - Coal tar polytherapy	379	150 to 630	0.771	0.752 to 0.788	15035	0%
Vit D OD - VPS BD - Coal tar polytherapy	379	150 to 628	0.771	0.752 to 0.788	15035	0%
Vit D BD - VPS OD - Coal tar polytherapy	380	152 to 621	0.771	0.752 to 0.788	15033	0%
Vit D BD - PS OD - TCF OD	394	150 to 702	0.771	0.752 to 0.788	15026	0%
PS OD - Vit D OD - Vit D BD	393	97 to 680	0.771	0.751 to 0.788	15023	0%
Vit D OD - PS OD - TCF OD	399	144 to 738	0.771	0.752 to 0.788	15021	0%
TCF - Vit D BD - VPS OD	438	279 to 676	0.773	0.755 to 0.789	15017	0%
VPS OD - Vit D OD - Referral	419	119 to 680	0.772	0.753 to 0.789	15017	0%
PS OD - Vit D BD - Coal Tar polytherapy	394	111 to 644	0.77	0.751 to 0.788	15016	0%
VPS OD - Vit D BD - Referral	421	124 to 670	0.772	0.753 to 0.789	15014	0%
PS OD - Vit D OD - Coal tar polytherapy	396	100 to 669	0.77	0.751 to 0.788	15013	0%
PS BD - Vit D BD - TCF OD	414	165 to 673	0.771	0.753 to 0.788	15010	0%
PS BD - Vit D OD - TCF OD	414	160 to 689	0.771	0.753 to 0.788	15009	0%
Vit D OD - Vit D BD - VPS OD	405	188 to 653	0.771	0.752 to 0.788	15007	0%
PS BD - TCF OD - Vit D BD	429	192 to 680	0.771	0.753 to 0.788	15001	0%
Vit D OD - PS BD - TCF OD	418	183 to 681	0.771	0.752 to 0.788	14998	0%
Vit D BD - PS BD - TCF OD	418	195 to 665	0.771	0.752 to 0.788	14997	0%
Vit D OD - PS OD - Vit D BD	404	152 to 672	0.77	0.751 to 0.788	14997	0%
TCF OD - PS BD - Vit D BD	449	280 to 661	0.772	0.754 to 0.789	14995	0%
PS BD - TCF OD - Coal Tar polytherapy	430	199 to 666	0.771	0.753 to 0.788	14994	0%
Vit D BD - PS OD - Coal Tar polytherapy	404	162 to 636	0.77	0.75 to 0.788	14989	0%
Vit D OD - TCF OD - VPS OD	444	232 to 711	0.772	0.753 to 0.788	14989	0%
TCF OD - PS BD - Coal Tar polytherapy	450	281 to 646	0.772	0.754 to 0.789	14988	0%
Vit D BD - TCF OD - VPS OD	445	252 to 694	0.772	0.754 to 0.788	14987	0%

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @ £20k (£)	Probability optimal @ £20k
Vit D OD - PS OD - Coal tar polytherapy	407	155 to 660	0.77	0.75 to 0.788	14987	0%
TCF OD - VPS OD - Referral	470	273 to 715	0.773	0.754 to 0.789	14983	0%
TCF OD - Vit D BD - PS BD	463	294 to 668	0.772	0.754 to 0.789	14978	0%
PS OD - TCF OD - Referral	453	129 to 760	0.771	0.752 to 0.788	14976	0%
PS BD - Vit D OD - Vit D BD	426	167 to 647	0.77	0.751 to 0.788	14975	0%
Vit D OD - Vit D BD - PS OD	426	189 to 676	0.77	0.75 to 0.788	14970	0%
Vit D OD - VPS OD - Referral	442	181 to 684	0.77	0.751 to 0.788	14964	0%
Vit D OD - VPS BD - Referral	442	183 to 682	0.77	0.751 to 0.788	14964	0%
Vit D OD - PS BD - Vit D BD	430	198 to 638	0.77	0.75 to 0.788	14964	0%
PS BD - Vit D OD - Coal Tar polytherapy	429	176 to 635	0.77	0.75 to 0.788	14963	0%
Vit D BD - VPS OD - Referral	444	186 to 673	0.77	0.751 to 0.788	14961	0%
PS BD - Vit D BD - Coal Tar polytherapy	432	179 to 627	0.77	0.75 to 0.788	14959	0%
Vit D OD - PS BD - Coal tar polytherapy	433	203 to 628	0.769	0.75 to 0.787	14952	0%
Vit D OD - TCF OD - PS BD	470	245 to 700	0.771	0.752 to 0.788	14950	0%
Vit D BD - TCF OD - PS BD	470	270 to 685	0.771	0.752 to 0.788	14948	0%
Vit D BD - PS BD - Coal Tar polytherapy	436	209 to 620	0.769	0.75 to 0.787	14947	0%
Vit D OD - Vit D BD - PS BD	447	224 to 643	0.77	0.75 to 0.788	14944	0%
PS OD - Vit D BD - Referral	461	157 to 686	0.77	0.75 to 0.788	14939	0%
PS OD - Vit D OD - Referral	462	133 to 707	0.77	0.75 to 0.788	14938	0%
PS BD - TCF OD - Referral	491	233 to 719	0.771	0.752 to 0.788	14926	0%
TCF OD - PS BD - Referral	511	317 to 699	0.772	0.753 to 0.788	14920	0%
Vit D BD - PS OD - Referral	472	210 to 677	0.769	0.749 to 0.787	14912	0%
Vit D OD - PS OD - Referral	473	192 to 697	0.769	0.749 to 0.787	14911	0%
TCF OD - Vit D BD - Coal Tar polytherapy	525	305 to 737	0.771	0.752 to 0.788	14901	0%
Vit D OD - Vit D BD - TCF OD	514	231 to 785	0.77	0.751 to 0.788	14890	0%
Vit D OD - TCF OD - Vit D BD	529	255 to 791	0.771	0.752 to 0.788	14881	0%
PS BD - Vit D OD - Referral	502	245 to 677	0.769	0.749 to 0.787	14880	0%
PS BD - Vit D BD - referral	506	254 to 672	0.769	0.749 to 0.787	14875	0%
Vit D OD - TCF OD - Coal Tar polytherapy	531	256 to 780	0.77	0.751 to 0.788	14872	0%
Vit D BD - TCF OD - Coal Tar polytherapy	532	287 to 755	0.77	0.751 to 0.788	14871	0%
Vit D OD - PS BD - Referral	506	270 to 669	0.769	0.749 to 0.787	14869	0%
Vit D BD - PS BD - Referral	510	285 to 664	0.769	0.749 to 0.787	14863	0%
Vit D OD - Vit D BD - Coal Tar polytherapy	532	257 to 717	0.768	0.748 to 0.787	14837	0%
TCF OD - Vit D BD - Referral	588	344 to 784	0.771	0.752 to 0.788	14830	0%
Vit D OD - TCF OD - Referral	593	289 to 822	0.77	0.75 to 0.788	14802	0%

Strategy (a)	Mean Cost (£)	95% CI (£)	Mean Benefit (QALYs)	95% CI (QALYs)	Mean NMB @ £20k (£)	Probability optimal @ £20k
Vit D BD - TCF OD - Referral	595	324 to 801	0.77	0.75 to 0.788	14800	0%
Capasal only	550	218 to 701	0.767	0.746 to 0.787	14783	0%
Vit D OD - Vit D BD - Referral	606	338 to 750	0.768	0.747 to 0.787	14752	0%
Vehicle only	612	575 to 649	0.765	0.744 to 0.786	14692	0%

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

Table 37: Disaggregated total costs by items of resource use

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
VPS OD - VPS BD - TCF OD	£85	£33	£21	£36	£175
PS OD - VPS OD - VPS BD	£40	£45	£25	£42	£152
VPS OD - VPS BD - Vit D OD	£60	£36	£32	£54	£183
VPS OD - VPS BD - Vit D BD	£60	£36	£32	£54	£182
VPS OD - VPS BD - Coal tar polytherapy	£49	£38	£36	£61	£184
PS BD - VPS OD - VPS BD	£43	£49	£28	£47	£166
PS OD - PS BD - VPS BD	£42	£50	£30	£52	£174
PS OD - VPS BD - TCF OD	£90	£41	£23	£40	£195
VPS OD - Vit D OD - VPS BD	£83	£44	£32	£54	£213
VPS OD - Vit D BD - VPS BD	£83	£44	£32	£54	£213
PS OD - VPS BD - Vit D BD	£62	£45	£35	£61	£204
PS OD - VPS BD - Vit D OD	£62	£45	£36	£61	£204
PS OD - VPS BD - Coal tar polytherapy	£49	£47	£40	£69	£205
VPS OD - VPS BD - Referral	£60	£35	£50	£82	£227
PS BD - VPS BD - TCF OD	£98	£45	£26	£45	£214
VPS OD - TCF OD - VPS BD	£160	£36	£21	£36	£254
VPS BD - Vit D BD - TCF OD	£138	£37	£31	£53	£258
VPS BD - Vit D OD - TCF OD	£139	£37	£31	£53	£259
PS BD - VPS BD - Vit D OD	£68	£49	£40	£68	£225
PS BD - VPS BD - Vit D BD	£68	£49	£40	£68	£224
VPS BD - TCF OD - Vit D BD	£153	£33	£31	£53	£269
PS OD - PS BD - VPS OD	£48	£53	£40	£69	£211
PS BD - VPS BD - Coal tar polytherapy	£53	£51	£45	£77	£226
VPS BD - TCF OD - Coal tar polytherapy	£141	£34	£35	£60	£271
PS OD - Vit D BD - VPS BD	£89	£54	£35	£61	£239
PS OD - Vit D OD - VPS BD	£89	£54	£36	£61	£239
Vit D OD - VPS OD - VPS BD	£93	£54	£32	£54	£233

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
Vit D BD - VPS OD - VPS BD	£94	£54	£32	£54	£233
VPS BD - Vit D OD - Vit D BD	£104	£42	£46	£79	£270
VPS BD - Vit D OD - Coal tar polytherapy	£87	£44	£52	£89	£273
VPS BD - Vit D BD - Coal tar polytherapy	£87	£44	£52	£89	£272
PS OD - VPS BD - Referral	£62	£44	£56	£93	£255
PS OD - VPS OD - TCF OD	£111	£47	£31	£54	£243
Vit D BD - PS OD - VPS BD	£93	£57	£35	£61	£246
Vit D OD - PS OD - VPS BD	£93	£57	£36	£61	£246
PS OD - TCF OD - VPS BD	£177	£45	£23	£40	£285
PS BD - Vit D OD - VPS BD	£96	£58	£40	£68	£262
PS BD - Vit D BD - VPS BD	£96	£58	£40	£68	£261
PS OD - VPS OD - Vit D BD	£75	£52	£47	£80	£255
PS OD - VPS OD - Vit D OD	£75	£52	£47	£81	£255
PS OD - VPS OD - Coal tar polytherapy	£58	£54	£54	£91	£257
VPS BD - TCF OD - Referral	£153	£32	£49	£82	£316
TCF OD - VPS OD - VPS BD	£210	£41	£21	£36	£308
Vit D OD - PS BD - VPS BD	£96	£60	£40	£68	£264
PS BD - VPS OD - TCF OD	£122	£51	£35	£60	£268
Vit D BD - PS BD - VPS BD	£96	£60	£40	£68	£263
PS BD - VPS BD - Referral	£67	£48	£62	£103	£280
Vit D BD - VPS BD - TCF OD	£157	£49	£31	£53	£290
PS BD - TCF OD - VPS BD	£191	£48	£26	£45	£311
PS OD - Vit D BD - VPS OD	£96	£58	£47	£80	£281
PS BD - VPS OD - Vit D OD	£82	£57	£53	£90	£282
PS BD - VPS OD - Vit D BD	£82	£57	£53	£90	£281
PS OD - Vit D OD - VPS OD	£96	£58	£47	£81	£282
TCF OD - PS BD - VPS BD	£211	£45	£26	£45	£327
PS OD - PS BD - TCF OD	£130	£53	£39	£67	£290
VPS BD - Vit D OD - Referral	£103	£40	£70	£116	£330
PS BD - VPS OD - Coal Tar polytherapy	£63	£59	£60	£102	£284
VPS BD - Vit D BD - Referral	£103	£40	£70	£116	£329
PS OD - TCF OD - VPS OD	£181	£47	£31	£54	£313
Vit D BD - VPS BD - Coal tar polytherapy	£106	£57	£52	£89	£304
TCF OD - VPS BD - Vit D BD	£229	£41	£31	£53	£353
Vit D BD - PS OD - VPS OD	£100	£61	£47	£80	£288
PS OD - PS BD - Vit D BD	£85	£60	£60	£102	£307
VPS OD - Vit D BD - TCF OD	£174	£46	£41	£70	£331
VPS OD - Vit D OD - TCF OD	£174	£46	£41	£70	£331
Vit D OD - PS OD - VPS OD	£100	£61	£47	£81	£289

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
TCF OD - VPS BD - Coal tar polytherapy	£218	£42	£35	£60	£355
PS OD - PS BD - Vit D OD	£85	£60	£60	£102	£308
VPS OD - TCF OD - Vit D BD	£191	£42	£41	£70	£343
PS OD - PS BD - Coal Tar polytherapy	£64	£63	£69	£116	£311
PS BD - Vit D OD - VPS OD	£104	£63	£53	£90	£309
PS OD - VPS OD - Referral	£75	£51	£73	£121	£319
PS BD - Vit D BD - VPS OD	£104	£63	£53	£90	£309
VPS OD - TCF OD - Coal tar polytherapy	£176	£44	£47	£80	£346
PS OD - Vit D BD - PS BD	£100	£62	£60	£102	£324
PS OD - TCF OD - PS BD	£183	£50	£39	£67	£340
Vit D OD - PS BD - VPS OD	£104	£64	£53	£90	£311
PS OD - Vit D OD - PS BD	£100	£62	£60	£102	£325
Vit D BD - PS BD - VPS OD	£104	£64	£53	£90	£311
VPS OD - Vit D OD - Vit D BD	£128	£53	£61	£104	£347
PS BD - TCF OD - VPS OD	£197	£51	£35	£60	£343
Vit D OD - Vit D BD - VPS BD	£152	£64	£46	£79	£341
VPS OD - Vit D OD - Coal Tar polytherapy	£107	£56	£69	£117	£350
TCF OD - PS BD - VPS OD	£216	£48	£35	£60	£359
VPS OD - Vit D BD - Coal Tar polytherapy	£107	£56	£69	£117	£349
TCF OD - Vit D BD - VPS BD	£253	£48	£31	£53	£385
Vit D BD - PS OD - PS BD	£104	£65	£60	£102	£331
Vit D OD - PS OD - PS BD	£104	£65	£60	£102	£332
PS BD - VPS OD - Referral	£82	£55	£80	£133	£350
TCF OD - VPS BD - Referral	£229	£39	£49	£82	£400
Vit D BD - VPS OD - TCF OD	£184	£56	£41	£70	£351
Vit D OD - VPS OD - TCF OD	£184	£56	£41	£70	£352
Vit D OD - VPS BD - TCF OD	£184	£56	£41	£70	£352
Vit D BD - VPS BD - Referral	£122	£53	£70	£116	£361
Vit D OD - TCF OD - VPS BD	£258	£54	£31	£53	£395
PS OD - Vit D BD - TCF OD	£191	£57	£46	£79	£373
Vit D BD - TCF OD - VPS BD	£258	£53	£31	£53	£395
VPS OD - TCF OD - Referral	£191	£40	£64	£107	£402
PS OD - Vit D OD - TCF OD	£191	£58	£46	£79	£374
TCF OD - VPS OD - Vit D BD	£240	£47	£41	£70	£398
PS OD - TCF OD - Vit D BD	£210	£52	£46	£79	£387
Vit D OD - VPS OD - Vit D BD	£139	£63	£61	£104	£367
Vit D OD - VPS BD - Vit D BD	£139	£63	£61	£104	£367
TCF OD - VPS OD - Coal tar polytherapy	£225	£49	£47	£80	£400

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
PS OD - TCF OD - Coal Tar polytherapy	£193	£55	£53	£90	£391
PS OD - PS BD - Referral	£85	£55	£92	£152	£383
Vit D OD - VPS OD - Coal tar polytherapy	£118	£66	£69	£117	£370
Vit D OD - VPS BD - Coal tar polytherapy	£118	£66	£69	£117	£370
Vit D BD - VPS OD - Coal tar polytherapy	£118	£66	£69	£117	£370
Vit D BD - PS OD - TCF OD	£195	£61	£46	£79	£380
PS OD - Vit D OD - Vit D BD	£139	£66	£70	£119	£394
Vit D OD - PS OD - TCF OD	£195	£61	£46	£79	£381
TCF - Vit D BD - VPS OD	£259	£52	£41	£70	£422
VPS OD - Vit D OD - Referral	£128	£52	£91	£149	£420
PS OD - Vit D BD - Coal Tar polytherapy	£115	£69	£80	£134	£398
VPS OD - Vit D BD - Referral	£128	£51	£91	£149	£419
PS OD - Vit D OD - Coal tar polytherapy	£115	£69	£80	£134	£399
PS BD - Vit D BD - TCF OD	£209	£63	£52	£88	£412
PS BD - Vit D OD - TCF OD	£209	£63	£52	£88	£412
Vit D OD - Vit D BD - VPS OD	£162	£69	£61	£104	£396
PS BD - TCF OD - Vit D BD	£229	£57	£52	£88	£426
Vit D OD - PS BD - TCF OD	£209	£64	£52	£88	£414
Vit D BD - PS BD - TCF OD	£209	£64	£52	£88	£413
Vit D OD - PS OD - Vit D BD	£143	£69	£70	£119	£401
TCF OD - PS BD - Vit D BD	£249	£54	£52	£88	£443
PS BD - TCF OD - Coal Tar polytherapy	£210	£60	£60	£101	£430
Vit D BD - PS OD - Coal Tar polytherapy	£119	£72	£80	£134	£405
Vit D OD - TCF OD - VPS OD	£264	£57	£41	£70	£433
TCF OD - PS BD - Coal Tar polytherapy	£230	£56	£60	£101	£446
Vit D BD - TCF OD - VPS OD	£264	£57	£41	£70	£432
Vit D OD - PS OD - Coal tar polytherapy	£119	£73	£80	£134	£406
TCF OD - VPS OD - Referral	£240	£45	£64	£107	£457
TCF OD - Vit D BD - PS BD	£263	£55	£52	£88	£459
PS OD - TCF OD - Referral	£210	£48	£73	£122	£453
PS BD - Vit D OD - Vit D BD	£152	£72	£79	£132	£435
Vit D OD - Vit D BD - PS OD	£162	£73	£70	£119	£424
Vit D OD - VPS OD - Referral	£139	£62	£91	£149	£440
Vit D OD - VPS BD - Referral	£139	£62	£91	£149	£440
Vit D OD - PS BD - Vit D BD	£152	£74	£79	£132	£437

Strategy	Topicals	Primary care	Specialist outpatient	Day Centre Care	Total (a)
PS BD - Vit D OD - Coal Tar polytherapy	£126	£76	£90	£150	£441
Vit D BD - VPS OD - Referral	£139	£62	£91	£149	£440
PS BD - Vit D BD - Coal Tar polytherapy	£125	£76	£89	£149	£440
Vit D OD - PS BD - Coal tar polytherapy	£126	£78	£90	£150	£443
Vit D OD - TCF OD - PS BD	£268	£61	£52	£88	£469
Vit D BD - TCF OD - PS BD	£268	£60	£52	£88	£468
Vit D BD - PS BD - Coal Tar polytherapy	£126	£77	£89	£149	£442
Vit D OD - Vit D BD - PS BD	£168	£76	£79	£132	£455
PS OD - Vit D BD - Referral	£139	£59	£104	£171	£473
PS OD - Vit D OD - Referral	£139	£59	£104	£171	£474
PS BD - TCF OD - Referral	£229	£52	£81	£134	£496
TCF OD - PS BD - Referral	£248	£49	£81	£134	£513
Vit D BD - PS OD - Referral	£143	£62	£104	£171	£480
Vit D OD - PS OD - Referral	£143	£62	£104	£171	£481
TCF OD - Vit D BD - Coal Tar polytherapy	£276	£62	£70	£117	£524
Vit D OD - Vit D BD - TCF OD	£282	£70	£61	£103	£515
Vit D OD - TCF OD - Vit D BD	£302	£64	£61	£103	£530
PS BD - Vit D OD - Referral	£152	£65	£114	£188	£519
PS BD - Vit D BD - referral	£152	£65	£114	£187	£518
Vit D OD - TCF OD - Coal Tar polytherapy	£281	£67	£70	£117	£535
Vit D BD - TCF OD - Coal Tar polytherapy	£281	£67	£70	£117	£534
Vit D OD - PS BD - Referral	£152	£66	£114	£188	£521
Vit D BD - PS BD - Referral	£152	£66	£114	£187	£520
Vit D OD - Vit D BD - Coal Tar polytherapy	£187	£85	£104	£172	£548
TCF OD - Vit D BD - Referral	£297	£53	£92	£152	£594
Vit D OD - TCF OD - Referral	£302	£58	£92	£152	£605
Vit D BD - TCF OD - Referral	£302	£58	£92	£152	£604
Capasal only	£118	£100	£131	£213	£562
Vit D OD - Vit D BD - Referral	£217	£72	£128	£209	£627
Vehicle only	£112	£109	£149	£238	£609

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

N.3.2 Sensitivity analyses

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

N.3.2.1 Restricted comparators

The base case analysis put a few conditions on the way topicals could be sequenced (see Table 24 in section N.2.1.1. These did not restrict how potent and very potent corticosteroids fit into treatment sequences. The GDG expressed concern that this lack of restrictions may not fully reflect the way these topicals are and should be used in general practice. They indicated that much more caution is and should be used when prescribing potent and very potent corticosteroids for both continuous and intermittent use. The GDG was also concerned that the analysis did not fully capture the safety risks associated with the use of these agents. In a stepwise fashion, various additional restrictions were placed on the use of these agents in each sequence. A summary of optimal strategies for all scenarios is presented in Table 38.

Scenario 1: In the first scenario, all strategies involving potent or very potent corticosteroids (including two compound formulation product) in all three lines of treatment were removed. The results confirmed the findings of the base case results in which once daily very potent corticosteroid then twice daily very potent corticosteroid was found to be most cost-effective as first and second-line treatments. However, in this scenario no further steroid could be prescribed; therefore vitamin D analogue was found to be the most cost-effective third line treatment, applied either once or twice daily.

Scenario 2: In the second scenario, no sequence could include the consecutive use of potent or very potent corticosteroid, including as part of TCF product. The results again showed the likely cost-effectiveness of strategies including potent and very potent corticosteroids. Here, starting with once daily very potent corticosteroids and then moving to once or twice daily vitamin D analogue and then twice daily very potent corticosteroids was least costly and second most effective. Starting the sequence with twice daily very potent corticosteroid and ending with once daily TCF product generated 0.00055 more QALYs, but at an additional cost of £45.20 per year. The resulting ICER (£82,182) is thus over the £20,000 per QALY threshold.

Scenario 3: In the third scenario, twice daily application of very potent corticosteroid could not precede once daily application. There were no changes to the base case results under these conditions.

Scenario 4: If the conditions outlined in scenarios 1 and 2 are combined and very potent corticosteroids were also restricted such that they could not appear first in a sequence, then the optimal strategy at a £20,000 per QALY threshold is to start with once daily potent corticosteroid, then move to twice daily vitamin D and end with once or twice daily very potent corticosteroid. Replacing first line potent steroid with once daily TCF product is expected to generate <0.0007 QALYs, but for an additional cost of around £145 (ICER>£200,000).

In addition to the concerns raised about the safety of potent and very potent corticosteroids, the GDG raised the issue of cosmetic acceptability and its importance in the treatment of scalp psoriasis. In particular, they voiced a strong preference for once daily application, stating that few patients would be willing or interested in applying topicals to their scalp more than once a day at night. On that basis, modelled comparators were restricted in a stepwise fashion. Results of these two scenarios are presented in Table 38.

Scenario 5: In the fifth scenario, twice daily strategies were reserved for second and third line treatment following failure of at least one once daily strategy. Under this scenario and combined with the restrictions outlined in scenario 4 above, the optimal sequence was once daily potent

corticosteroids followed by once or twice daily vitamin D, and ending with once or twice daily very potent corticosteroid.

Replacing initial potent corticosteroids with once daily TCF product in this sequence would increase benefits (0.00058 QALYs) but also increase cost (£147) at a ratio of £253,621 per QALY gained. Similarly, replacing second line vitamin D analogue with once daily TCF product would produce additional QALY gains (approximately 0.001), but at extra cost (approximately £40), producing ICERs around £40,000 per QALY gained.

Scenario 6: In a final scenario, all twice daily strategies were removed and only sequences of once daily treatments were included. If steroids could be offered anywhere in the sequence, then the most cost-effective strategy was to start with potent corticosteroids, move up to very potent corticosteroids and then try TCF product if both steroids alone have failed. If one wishes to avoid consecutive use of steroids, then the optimal strategy is to start with potent steroids, then switch to vitamin D analogues and end with very potent corticosteroids. Replacing very potent corticosteroids with TCF product in this sequence generates 0.00132 more QALYs, but with an ICER too high to be considered cost-effective (ICER=£39,773).

Table 38: Top ten treatment sequences across restricted comparator scenarios, ranked by greatest NMB at £20,000 threshold

Rank	Scenario 1	Scenario 2	Scenario 4	Scenario 5	Scenario 6
1	VPS OD - VPS BD - Vit D OD	VPS OD - Vit D OD - VPS BD	PS OD - Vit D BD - VPS BD	PS OD - Vit D BD - VPS BD	PS OD - VPS OD - TCF OD
2	VPS OD - VPS BD - Vit D BD	VPS OD - Vit D BD - VPS BD	PS OD - Vit D OD - VPS BD	PS OD - Vit D OD - VPS BD	PS OD - VPS OD - Vit D OD
3	VPS OD - VPS BD - Coal tar	VPS BD - Vit D BD - TCF OD	PS BD - Vit D OD - VPS BD	PS OD - Vit D BD - VPS OD	PS OD - VPS OD - Coal tar
4	VPS OD - Vit D OD - VPS BD	VPS BD - Vit D OD - TCF OD	PS BD - Vit D BD - VPS BD	PS OD - Vit D OD - VPS OD	PS OD - Vit D OD - VPS OD
5	VPS OD - Vit D BD - VPS BD	PS OD - Vit D BD - VPS BD	PS OD - Vit D BD - VPS OD	PS OD - Vit D BD - PS BD	PS OD - TCF OD - VPS OD
6	PS OD - VPS BD - Vit D BD	PS OD - Vit D OD - VPS BD	PS OD - Vit D OD - VPS OD	PS OD - Vit D OD - PS BD	VPS OD - Vit D OD - TCF OD
7	PS OD - VPS BD - Vit D OD	VPS BD - Vit D OD - Vit D BD	Vit D BD - VPS BD - Coal tar	Vit D OD - Vit D BD - VPS BD	Vit D OD - PS OD - VPS OD
8	PS OD - VPS BD - Coal tar	VPS BD - Vit D OD - Coal tar	PS BD - Vit D OD - VPS OD	TCF OD - Vit D BD - VPS BD	PS OD - VPS OD - Referral
9	VPS OD - VPS BD - Referral	VPS BD - Vit D BD - Coal tar	PS BD - Vit D BD - VPS OD	PS OD - Vit D BD - TCF OD	VPS OD - TCF OD - Coal tar
10	VPS BD - Vit D BD - TCF OD	PS BD - Vit D OD - VPS BD	PS OD - Vit D BD - PS BD	PS OD - Vit D OD - TCF OD	VPS OD - Vit D OD - Coal Tar

N.3.2.2 Variation in early and late response

The base case assumed that patients would trial a given topical for up to 8 weeks (maximum 4 weeks for very potent corticosteroids). Some proportion would be expected to respond by 4 weeks, and discontinue treatment at that time. The remainder would carry on to 8 weeks, at which time non-responders would move on to the next topical in a sequence. The data defining the breakdown of early (at 4 weeks) vs late (at 8 weeks) responders came from three studies[51,55,77] and was thus uncertain. Deterministic sensitivity analyses were performed around these parameters to observe the impact on the results.

First, an analysis was performed in which no one was expected to respond and discontinue treatment at 4 weeks (i.e. all responders require 8 weeks treatment). Compared to the results of the base case when all comparators are included, the ICER for once and then twice daily very potent corticosteroids followed by once daily TCF product increased to over £20,000 per QALY, making once daily potent corticosteroids followed by once and then twice daily very potent corticosteroids the optimal sequence. No changes to the conclusions of the more restrictive scenario 5 were observed (i.e. once daily potent corticosteroids then once or twice daily vitamin D followed by once or twice daily very potent corticosteroid is still optimal).

Second, an analysis was performed in which all responders were assumed to respond by 4 weeks, with no one requiring an additional 4 weeks of treatment. Small reductions in total cost and small improvements in total benefits were observed, but no significant changes to the results of the base case were observed.

Finally, an analysis was performed in which a 4-week stopping rule was applied. In this scenario, responders were limited to those that have responded by week 4 (see Table 13), and all other patients are assumed to move on to the next topical in the sequence (i.e. no one continues to 8 weeks of treatment with the same topical). The results of the base case were only somewhat sensitive to this stopping rule, with total costs and benefits improving slightly. Third line TCF product after once and twice daily very potent corticosteroids became even more cost-effective than in the base case. In the context of scenario 5, however, third line TCF product instead of once or twice daily very potent corticosteroids is still too costly relative to its added benefit to represent good value for NHS resource given the NICE threshold of £20,000.

N.3.2.3 Reduced adherence

There was some concern that issues of treatment adherence were inadequately captured in the model. The estimates of effect used in the base case were derived from randomised controlled trials which may represent the best case scenario for topical therapies. The GDG wished to explore how reduced adherence to twice daily treatments would affect the conclusions of the base case. In this scenario, 60%[74] of patients being treated with twice daily topical were assumed to adhere to treatment whilst the remaining 40% of patients were assumed to apply the topical only once daily. Thus, efficacy of the treatment would be reduced compared to the base case estimates. To be conservative, no reductions in cost were assumed despite the fact that less topical would be used.

With adherence reduced, the optimal strategy when all 169 comparators were included was once daily potent corticosteroid followed by once and then twice daily very potent corticosteroid. This was the second most cost-effective strategy in the base case. When considering only strategies included in Scenario 5 above, conclusions do not change. Once daily potent corticosteroid followed by once or twice daily vitamin D and then once or twice daily very potent corticosteroids is still optimal at a £20,000 threshold.

N.3.2.4 Lower expected resource use for TCF product

The base case of this analysis assumed that patient using TCF product for 4 weeks would use approximately 71.4 g of product. This estimate was based on the mean across five RCTs[46,50,54,55,77]. In a recent UK cost-utility analysis, Affleck and colleagues[76] assumed the 4-week quantity used to be 60 g. At this quantity, the unit cost of TCF product is cut nearly in half. This value was used in a sensitivity analysis to explore how sensitivity the results were to this particular value. This was quite a favourable scenario for TCF product as costs were reduced without assuming any commiserate reduction in efficacy by using less topical.

The results suggest that the base case conclusions, for which all sequences are included, do not change when the dose of TCF is fixed at 60 g. Here, as in the base case, the most effective and cost-

effective strategy places once daily TCF product as a third line treatment after trials of once and then twice daily very potent corticosteroid. The ICER comes down to under £1,000 in this sensitivity analysis compared to just over £19,000 in the base case.

Conclusions from the various scenarios in which most comparators are removed from the analysis for reasons of safety and patient preference (Scenario 5), appear to be somewhat sensitive to reductions in assumed dose of TCF product.

First line use of TCF product is still unlikely to represent better value for NHS resources than potent corticosteroids alone. To replace once daily potent corticosteroids with once daily TCF product as first line in a sequence followed by once or twice daily vitamin D analogue and then once or twice daily very potent corticosteroids would cost more than £70,000 per additional QALY gained. Although this is lower than the ICERs when base case dosing assumptions are in effect (ICERs >£180,000), it is still not low enough to be considered cost-effective given the NICE willingness to pay threshold.

Under base case dosing assumptions, as a second line strategy after once daily potent corticosteroid once daily TCF product was unlikely to be cost-effective compared to second line once and twice daily vitamin D (ICERs >£30,000 per QALY). When usage is assumed not to exceed 60 g per 4 weeks, then second line once daily TCF product is likely to dominate (be less costly and more effective than) once and twice daily vitamin D. Finally, when only once daily treatments are considered, as in scenario 6 above, reduced 4-week usage of TCF product brings the ICER of third line TCF product compared to very potent corticosteroid (following potent steroid and vitamin D) down to £5,279 compared to £39,733.

N.3.2.5 Unit costs of potent corticosteroids

The base case assumed that the cost for each topical was based on the product and scalp formulation with the lowest unit cost per gram/millilitre. Given that clinicians and patients may have preferences for different products or formulations, it was considered necessary to explore how variation in price of topicals, particularly potent corticosteroids, might affect the results. To do this, the highest cost (per gram) potent corticosteroid Synalar gel (fluocinolone acetonide) was assumed in place of Betacap scalp application. The cost of Synalar gel is around 4.6 times that of Betacap scalp application.

Under this costing assumption and considering all comparators, the sequence of once then twice daily very potent corticosteroid followed by once daily TCF product becomes the most effective and least costly. It is now less costly than the strategy starting with potent corticosteroids and then escalating up to once then twice daily very potent corticosteroids.

Additionally, the results of scenario 5, in which twice daily treatments and very potent corticosteroids are reserved for second and third line treatment and corticosteroids cannot be used consecutively , were insensitive to increased costs. The strategy of starting with once daily potent corticosteroid followed by once or twice vitamin D and then finally once or twice daily very potent corticosteroid remains the optimal choice given a £20,000 per QALY threshold.

N.3.2.6 Time horizon

A one year time horizon was used in the base case on the basis that little is known about the longer term efficacy, adherence and course of moderate to severe scalp psoriasis. Aware the psoriasis, including scalp psoriasis, is a chronic and long term condition, the GDG chose to explore how the results might be affected by lengthening the model time horizon to 2, 3 and 5 years. The results of the base case where all 169 comparators are included, appear somewhat sensitive to changes in the time horizon. The most effective and cost-effective strategy in the base case (once and then twice

daily very potent corticosteroid followed by once daily TCF product) is still most effective at 2, 3 and 5 years; however, its ICER relative to the least cost and second most effective sequence (once daily potent corticosteroid followed by once and then twice daily very potent corticosteroid) increases to values over the £20,000 threshold (£39,000, £56,000 and £73,000 at 2, 3 and 5 years respectively).

The results of scenarios 5 and 6 (as outlined above), wherein comparators are restricted in certain ways, are insensitive to extensions of the time horizon. Once daily potent corticosteroid followed by once or twice daily vitamin D and then once or twice daily very potent corticosteroid are still optimal.

N.4 Discussion

N.4.1 Summary of results

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

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

- Once daily potent corticosteroid is likely to be the optimal first line treatment if very potent corticosteroids are considered too aggressive.
- Once or twice daily vitamin D or analogues are likely to be cost-effective second in the sequence, after trials of potent or very potent corticosteroids, particularly where continuous corticosteroids are to be avoided
- Once or twice daily very potent corticosteroids is likely to be the most cost-effective third line treatment if potent corticosteroid and vitamin D have not worked
- TCF product may be cost-effective, but only after potent and/or very potent corticosteroids have failed and when only once daily applications of topicals is being considered

In general, sequences including once daily TCF product were slightly more effective than the same sequence including alternatives such as vitamin D analogue or potent corticosteroid; however, the very modest additional benefits (<0.001 and dependent on comparator) would only be considered potentially cost-effective if willingness to pay thresholds were substantially greater than £20,000 per QALY gained. If, however, the amount of TCF product used by patients is less than reported in the clinical trial evidence, such that a single 60 g pack is needed for 4 weeks, then TCF product may be cost-effective as a second or third line treatment following potent corticosteroids. Under no conditions was first line use of TCF product likely to represent better value for NHS resources than potent or very potent corticosteroids.

N.4.2 Limitations & interpretation

The analysis presented here has several limitations which were considered carefully by the GDG. Firstly, the analysis evaluates treatment sequences even though the available trial data compares single topicals head to head without sequencing. In order to apply the treatment effects within the

sequencing model, we assumed that treatment effects were independent. That is, we assumed the effectiveness of TCF product as a second or third line topical was equal to its effectiveness as a first line agent and that this was true regardless of other topicals it may follow. The GDG did not believe this to be a significant limitation given that the patients included in the overwhelming majority of RCTs were reported to have psoriasis for longer than 5 years, during which they can be assumed to have previously tried, succeeded and/or failed various topical treatments.

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

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

The model also takes a relatively short time horizon considering that psoriasis of the scalp is a chronic, long term condition for which patients may take up treatment intermittently for many years of their lives. Frequency and severity of relapse, selection for and speed of onward referral, methods of self-management and long-term safety are all issues inadequately addressed in the evidence base and therefore translate into limitations of the economic analysis. Longer time horizons of up to 5 years were explored in sensitivity analyses and conclusions were insensitive to these extensions.

The model estimated the health gain for each treatment by mapping the change in PASI score to the EQ-5D based on observational evidence. However, it has been noted that several important areas of health-related quality of life for people with psoriasis are not directly assessed by the EQ-5D questionnaire[75]. Therefore it is possible that the EQ-5D may lack content validity for these patients. Research is ongoing in this area. But we note that even using a £30,000 per QALY threshold rather than £20,000 would not change the conclusions of our analyses. Therefore only if the EQ-5D is under-estimating health gain of one treatment compared to another by a considerable extent, could this pose a serious limitation.

Considering both the strengths and weakness of the analysis, the GDG used it to inform their recommendations on the treatment of scalp psoriasis. The analysis showed that there were relatively small differences in terms of benefit between different topical sequences for scalp psoriasis, but large differences in terms of cost. Based on the mean costs and benefits of 169 compared sequences, the analysis found that initial treatment with once daily very potent corticosteroids is likely to offer the best value for NHS resource; however, the GDG was concerned that very potent corticosteroids, although effective and cost-effective, are quite an aggressive strategy and carry greater risk of steroid-related adverse events, which were not captured in the economic model. The second most cost-effective first line treatment in the base case and across a range of sensitivity and scenario analyses was once daily potent corticosteroids.

Following initial treatment with once daily potent corticosteroids, either once daily very potent corticosteroid, once or twice daily vitamin D analogue or once daily TCF product (only if mean quantity of topical used is under 60 g per month) would likely represent cost-effective second line choices. The GDG considered it important to think about avoiding the continuous use of corticosteroids (potent or very potent), and on the basis of results from scenarios 4 and 5, found vitamin D or analogue likely to represent the optimal second line choice. However, if a product with steroids was considered necessary and appropriate, they felt once daily TCF product would represent a safer alternative than very potent corticosteroid.

If these topicals fail to bring about control of scalp psoriasis, then the optimal third-line treatment is twice daily very potent corticosteroids. It was considered appropriate as third-line treatment, as the

number of patients exposed to the risks would be fewer but the need for efficacy more urgent. The GDG noted strong patient preference for once daily applications due to the messiness, inconvenience and cosmetic acceptability of topicals applied to the scalp. Therefore, if escalation to twice daily very potent corticosteroids was considered unacceptable, then once daily very potent corticosteroid is likely offer the next best value for NHS resource.

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

N.4.3 Generalisability to other populations / settings

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

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

N.4.4 Comparisons with published studies

The findings from the NCGC original economic analysis are quite different from the results of the most similar published study by Affleck and colleagues[76]. Affleck and colleagues found a sequence starting with twice daily potent corticosteroids followed by concurrent treatment (am/pm) with vitamin D analogue and potent corticosteroid and then once daily TCF product to be most cost-effective. Although the analysis appears to have been executed well, the included comparators and the estimates of effect and resource use had limitations which called the conclusions of the analysis into question.

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

management for the treatment of the trunks and limbs, they constitute a reasonable, short-term option for treating the scalp.

The second key difference between the analyses relates to the relative treatment effects used. Affleck and colleagues derived their treatment effects from an adjusted indirect comparison[78], which, when compared to the NCGC network meta-analysis, appears to have overestimated the effectiveness of TCF product compared to other topicals. For example, in their analysis TCF product was found to be 2.45 times more likely to induce response than once daily calcipotriol (RR=2.45, 95% CI: 1.84 to 3.27). The NCGC network meta-analysis found the risk ratio to be lower, around 1.857. This translates into an absolute risk difference between the two comparators of 35.54% using Affleck's estimates and 29.65% using the NCGC estimates. Differences such as these add up when synthesised in economic models and could lead to biased conclusions.

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

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

N.4.5 Conclusion

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

The most consistently cost-effective first line treatment when very potent corticosteroids were excluded was once daily potent corticosteroid. This conclusion was robust to the majority of sensitivity and scenario analyses undertaken.

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

- Sensitivity analyses in which continuous or consecutive use of topicals containing steroids was restricted found that once and twice daily vitamin D analogues are cost-effective as second line treatments in sequences with potent and very potent corticosteroids.
- Sensitivity analyses in which only once daily applications were considered found that initial treatment with potent steroids was optimal, followed by either very potent corticosteroid and then two-compound formulation product if steroids could be used continuously or followed by vitamin D analogue and very potent corticosteroid if continued use of steroids was to be avoided.

N.4.6 Implications for future research

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

Appendix O:Cost-effectiveness analysis – Second line biologic therapy

O.1 Introduction

There are many cost-effectiveness analyses in the published literature assessing the value of biologic therapies in a biologic naïve population; however, no cost-effectiveness analyses were identified that evaluated these treatments in a population with previous biologic exposure. There was some evidence from observational data presented in the clinical review (see Chapter 20) to suggest that biologic therapies might be slightly less effective in a population with previous exposure than in a biologic naïve population; however, the same clinical review also identified randomised controlled trial evidence to suggest that biologic therapies were still much more effective than placebo. On this basis, the GDG considered it inappropriate to assume that the economic evaluations for biologic naïve patients were wholly applicable to a previously exposed population; therefore, uncertainty in the cost-effectiveness of second line biologic therapy remained.

The GDG was also aware that there is variable interpretation of existing NICE guidance [79-82] regarding the use of biologic therapies in psoriasis, meaning that switching biologic therapies is quite common in some areas of the country and not in others. The GDG was also mindful that the group of patients likely to reach this point in the care pathway is quite small, but that the quality of life implications for these individuals is profound. Due to this lingering uncertainty and the importance of this area in clinical practice, the GDG considered the development of an original cost-effectiveness model to evaluate switching to a second biologic therapy to be a high priority. The decision modelling presented here was developed in close collaboration between the health economist, the NCGC technical team and GDG members.

O.2 Methods

O.2.1 Model overview

The analysis set out to evaluate the cost-effectiveness of switching to a second biologic therapy compared to best supportive care for patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biologic therapy. A cost-utility analysis was undertaken in line with the methods of the NICE reference case [83]. QALYs were calculated using utility weights from EQ-5D responses and UK public valuations. Costs were considered from a UK National Health Service and Personal Social Services perspective and expressed in 2011 UK sterling. Healthcare costs associated with starting and maintaining biologic therapy, as well as longer term costs of failing biologic therapy, were all included in the model.

The cost-effectiveness analysis must be relevant for decision-making over the longer term, as most people with psoriasis can be expected to require treatment for much of their lives. However, the evidence available for biological therapies is of short term duration and certain assumptions were made in order to extrapolate for many years beyond treatment initiation. A 10-year time horizon was considered sufficiently long enough to capture the relevant costs and benefits associated with both comparators.

Evidence of effectiveness for licensed biologic therapies, including adalimumab, etanercept, infliximab and ustekinumab was sparse for the subgroup of patients who have been previously treated with biologic therapy. In order to use all available data, the analysis assumed a class effect

for biologic therapy and therefore pooled the results for any biologic therapy compared to placebo. This was performed as part of a meta-analysis using an ordered probit model, which enabled the estimation of probabilities for achieving different levels of PASI response, including PASI50, PASI75 and PASI90.

The performance of alternative strategies was estimated using incremental cost-effectiveness ratios (ICERs), defined as the added cost of a given strategy divided by its added benefit compared with the next most expensive strategy. A threshold of £20,000 per QALY gained was used to assess cost-effectiveness although a threshold of up to £30,000 per QALY gained was explored in sensitivity analyses.

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

O.2.1.1 Comparators

The aim of the analysis was to assess the cost-effectiveness of biologic therapy compared to best supportive care in the treatment of patients with moderate to severe chronic plaque psoriasis who have previously received treatment with a biologic therapy. Due to a scarcity of data for specific biologic therapies licensed for the treatment of psoriasis - adalimumab, etanercept, infliximab and ustekinumab - the analysis assumes a class effect for biologic agents. Therefore, the analysis does not aim to look at particular sequences of biologic agents, nor can it inform recommendations for any particular choice of biologic agents.

O.2.1.2 Population

The population consists of patients with moderate to severe chronic plaque psoriasis who have been previously treated with biologic therapy. The clinical data available to inform the economic analysis did not allow for subgroup analyses to be performed based on the reason for failure of previous biologic therapy. Therefore, the overall population modelled includes primary non-responders (i.e. patients who had an insufficient response to previous biologic), secondary non-responders (i.e. patients who initially responded to previous biologic therapy but lost that response over time) and patients who were intolerant to previous biologic therapy.

O.2.1.3 Time horizon, perspective, discount rates used

The analysis took a UK National Health Service and Personal Social Services costing perspective, with costs expressed in 2011 UK sterling. A 10-year time horizon was considered clinically relevant and sufficiently long enough to capture important costs and consequences of biologic treatment. Future costs and benefits were discounted at a rate of 3.5% per annum.

O.2.2 Approach to modelling

O.2.2.1 Model structure

A two-part model was constructed in TreeAge Pro 2009 to capture the different costs and effects associated with biologic therapy and best supportive care. The structure of the model was adapted

from the model developed by Woolacott and colleagues[84] which has been used to inform related NICE guidance[79] and was validated by the GDG as a reasonable reflection of clinical practice.

For the biologic therapy arm, there was assumed to be a short 'trial' period, during which all hypothetical patients receive treatment and some level of benefit from treatment, and a 'treatment' period, during which only a subset of responders continue treatment and receive benefit.

'Trial' period:

- Hypothetical patients enter the model and receive a biologic therapy for an initial 'trial period.'
- During this 'trial period' they achieve a given level of PASI response (<PASI50, PASI50 to PASI75, PASI75 to PASI90, >PASI90) defined by the probabilities pPASI00, pPASI50, pPASI75, pPASI90 in Figure 355.

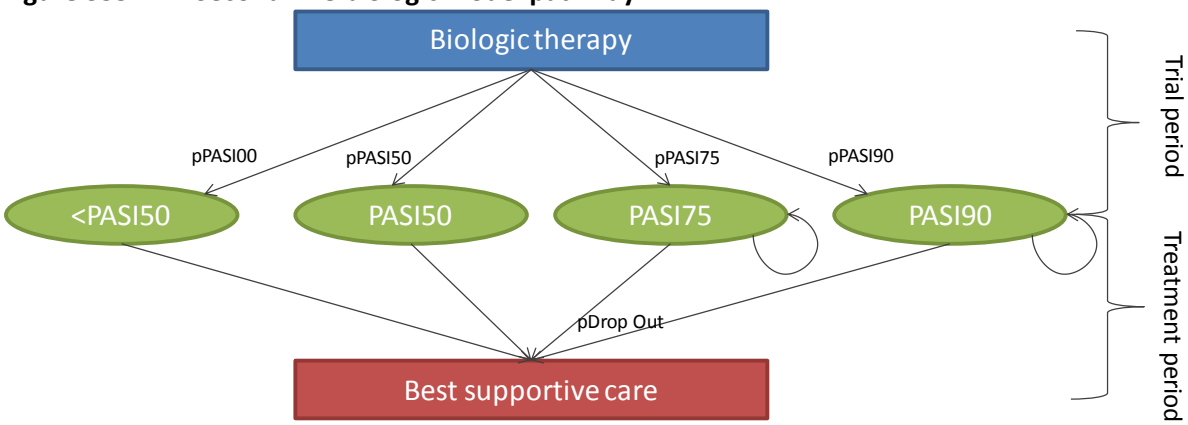
'Treatment' period:

- Patients who achieved a response >PASI75 during the trial period continue treatment and maintain that level of response until they drop out at some point in the future according to the probability pDrop Out in Figure 355.
- Patients who achieve a response of <PASI75 during the trial period discontinue treatment and move to best supportive care.

Key structural assumptions:

- Patients only receive benefit while they receive treatment, which is based on the assumption that treatments do not alter the progression of the disease
- Patients receiving treatment in the long term make no transitions between different levels of PASI response (i.e. they are assumed to maintain the same level of response observed at the end of the 'trial' period)

Figure 355: Second-line biologic model pathway



Patients on best supportive care may also achieve various levels of PASI response, which they are assumed to maintain until the end of the model. The model assumes no difference between treatments in terms of mortality.

O.2.2.2 Uncertainty

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

was randomly selected from its specific probability distribution simultaneously and costs and QALYs were calculated using these random values. The model is run repeatedly – in this case 10,000 times – and results are summarised as mean costs and mean QALYs. Probability distributions in the analysis were based on error estimates from data sources, such as confidence intervals. In addition, a series of one-way and two-way sensitivity analyses were run in order to test the effect of certain structural or variable uncertainties.

O.2.3 Model inputs

O.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 9 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 39: Model specification

Input	Data	Source
Comparators	• Best supportive care • Biologic therapy	
Population	Individuals with moderate to severe plaque psoriasis who have been previously exposed to biologic therapy	
Perspective	UK NHS and & PSS	NICE reference case[63]
Time horizon	10 years	
Discounting	3.5% for costs; 3.5% for benefits	NICE reference case[63]

O.2.3.2 Baseline event rates

In the base case analysis, placebo response rates from the included randomised controlled trials were used to determine the effectiveness of patients receiving best supportive care (Table 41). The effect of this assumption was tested in a series of one-way sensitivity analyses in which the effectiveness of best supportive care was varied:

- Scenario 1: effectiveness assumed to be zero, i.e. no one receiving best supportive care achieved a PASI50 or higher
- Scenario 2: effectiveness based on observations from Woods 2008 wherein 65% of people admitted for inpatient treatment with baseline PASI10 to 20 achieved PASI50
- Scenario 3: effectiveness based on observations from Woods 2008 wherein 83% of people admitted for inpatient treatment with baseline >PASI20 achieved PASI50.

O.2.3.3 Relative treatment effects

The predicted response rates used in the model were derived from a pairwise meta-analysis of relevant subgroup data from three RCTs presented in the clinical evidence review (see Chapter 20). To allow a complete and coherent comparison to be made between biologic therapies and placebo, a fixed-effects ordered probit model was used to jointly model the different trial outcomes. The meta-analysis provided estimates of response for an average biologic therapy based on all observed data reported for any level of PASI response.

This method, reported in greater detail by Woolacott and colleagues[84], relies on two assumptions:

- That the treatment effects are constant across end-points on the probit scale
- That the treatment effects can be considered exchangeable between the trials

Table 40 presents the data from the RCTs which were included in the meta-analysis for biologic therapy compared to placebo.

Table 40: Response data extracted from the clinical trials and used in meta-analysis (numbers of patients)

Trial	Intervention	PASI response category				n=	Control	PASI response category				n=
		<50	50-75	75-90	90<			<50	50-75	75-90	90<	
PHOENIX1	Ustekinumab	41	43	53	75	212	Placebo	103	2	0	0	105
PHOENIX2	Ustekinumab	37	55	64	94	250	Placebo	116	4	3	1	124
Menter 2007	Infliximab	26		68		94	Placebo	27		0		27

Table 41 summarises the results of the meta-analysis in terms of absolute response rates and relative effects. In terms of mean response rates, biologic therapy is superior to placebo across all levels of PASI response. Based on these estimates, approximately 57% of patients receiving biologic therapy will achieve at least a PASI75 and continue treatment after the 'trial' period. Based on the estimates of response for placebo, regarded as representing 'best supportive care,' benefits are expected to be very small, with under 4% of patients achieving a PASI50 and less than 1% and 0.5% achieving a PASI75 and PASI90, respectively.

Table 41: Results of meta-analysis and summary of treatment effects used in model base case

	Probability of response			Risk ratio		
	Median	2.5% CI	97.5% CI	Median	2.5% CI	97.5% CI
Response = PASI50						
Best supportive care	3.8%	3.3%	4.4%	1.0	1.0	1.0
Biologic therapy	79.4%	70.4%	86.7%	20.7	17.7	24.0
Response = PASI75						
Best supportive care	0.8%	0.6%	1.1%	1.0	1.0	1.0
Biologic therapy	57.3%	46.1%	68.2%	71.1	50.4	102.4
Response = PASI90						
Best supportive care	0.1%	0.1%	0.2%	1.0	1.0	1.0
Biologic therapy	31.9%	22.6%	43.0%	287.7	173.0	485.2

Uncertainty in the response rates was captured by exporting the simulated posterior distribution from the Markov Chain Monte Carlo analysis in WinBUGS to the cost-effectiveness model, thus preserving any correlations.

It is important to note that this analysis is limited by the data available. Firstly, only data for infliximab and ustekinumab are available from randomised controlled trial evidence. It is unclear whether these values are likely to be an over or underestimate of likely response to etanercept and adalimumab in this subgroup of patients. Secondly, this analysis only draws conclusions regarding short term use, which is less than ideal for the treatment of a chronic, life-long condition.

O.2.3.4 Utilities

Achievement of different levels of PASI response and associated utility gain was used in the model to determine the impact of biological therapy on overall health. Estimates of utility gain were taken from a variety of sources, but for the base case values were taken from the cost-utility analysis conducted by Woolacott and colleagues[84], which were estimated from an analysis of data from etanercept trials and the HODaR Database (http://www.hodar.co.uk/). The authors estimated mean utility gain across 'all patients' regardless of baseline quality of life and for a subgroup of patients with the worst baseline quality of life (fourth quartile DLQI). The mean utility gains for 'all patients' were used in the base case (see Table 42) and gains for those with the worst baseline DLQI were used in a sensitivity analysis. In a further three sensitivity analyses, utility gain estimates that were used in other models[81,82] informing NICE guidance were used. All estimates of utility gain are presented in Table 43.

Table 42: Estimated utility gains for different PASI response categories used in the base case

	Gains in utility: mean	
PASI Response category	**Base case (SE)**	**Distribution parameters (c)**
<50	0.05 (0.01)	Gamma: α=25, β=0.002
≥50 and <75	0.17 (0.04)	Gamma: α=8.471, β=0.014 (d)
≥75 and <90	0.19 (0.04)	Gamma: α=0.125, β=0.16 (e)
≥90	0.21 (0.05)	Gamma: α=0.098, β=0.205 (f)

(c) Utility gains were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically (i.e. such that achieving PASI90 was always better than PASI70, which was always better than PASI50 and no response). Error estimates as above were used where available from the literature and where not (as in the case of the values from the adalimumab and ustekinumab STAs), utility gains were entered deterministically.

(d) Distribution mean = 0.12, which was added to the utility gain for <PASI50 (0.05+0.12=0.17)

(e) Distribution mean = 0.02, which was added to the utility gain for ≥PASI50 and <PASI75 (0.17+0.02=0.19)

(f) Distribution mean = 0.02, which was added to the utility gain for ≥PASI75 and <PASI90 (0.19+0.02=0.21)

Table 43: Estimated utility gains for different PASI response categories used in sensitivity analyses

	Gains in utility: mean				
PASI Response category	**4th Quartile DLQI (SE)**	**Distribution parameters for 4th Quartile DLQI (a)**	**Adalimumab STA[81] (EQ-5D)**	**Ustekinumab STA[82] (DLQI)**	**Ustekinumab STA[82] (SF-36)**
<50	0.12 (0.03)	Gamma: α=16, β=0.0075	0.063	0.04	0.0016
≥50 and <75	0.29 (0.06)	Gamma: α=6.422, β=0.0264 (b)	0.178	0.17	0.0424
≥75 and <90	0.38 (0.08)	Gamma: α=0.81, β=0.111 (c)	0.178	0.22	0.0970
≥90	0.41 (0.09)	Gamma: α=0.062, β=0.483 (d)	0.308	0.25	0.1276

(a) Utility gains were built into the model using gamma distributions around difference from next better health state to ensure the health state utilities added up logically. Error estimates as above were used where available and where not (as in the case of the values from the adalimumab and ustekinumab STAs), utility gains were entered deterministically.

(b) Distribution mean = 0.17, which was added to the utility gain for <PASI50 (0.12+0.17=0.29)

(c) Distribution mean = 0.09, which was added to the utility gain for ≥PASI50 and <PASI75 (0.29+0.09=0.38)

(d) Distribution mean = 0.03, which was added to the utility gain for ≥PASI75 and <PASI90 (0.38+0.03=0.41)

O.2.3.5 Resource use and cost

Only direct health care costs were assessed, and these included the cost of drugs and their administration and monitoring and the cost of outpatient visits, day centre care visits and inpatient

stays. The cost of tests undertaken to screen patients for eligibility of treatment was excluded from the analysis. Also excluded were the costs of treating adverse events, due to a lack of data of their impact on treatment pathways and resource use.

This section is broken into four parts. The first section focuses on resource use and costing information related to the drugs themselves. The second and third sections focus on parameters of resource use and unit costs included in the 'trial' period and 'treatment' period of biologic therapy, respectively. Finally, the fourth section presents the estimates of resource use and cost used to define best supportive care.

Note that the unit costs for inpatient stays, outpatient consultations, phototherapy and day care centre visits were each calculated as a weighted mean of several NHS reference cost components. Relative weights applied to each component were based on the activity level reported in the NHS reference cost schedule 2009-10. We assumed that the interquartile range for any given NHS reference cost fit a gamma distribution. Based on that assumption, we took the mean and manually adjusted the standard error estimate to calculate alpha and beta parameters for a gamma distribution that would come closest to reproducing the interquartile range reported in the NHS reference costs schedule. For the probabilistic analysis, each cost component was varied, multiplied by its relative weight and then summed with other cost components to equal the total unit cost for a given service.

Drug treatment

Drug dosages, administration schedules and unit costs were based on information from the BNF 62[85] and are presented in Table 44.

Table 44: Drugs: Dosages, administration schedules and unit costs

Drug	Dosage and schedule	Price per mg	Price per table/vial	Source
Ciclosporin (100 mg)	300 mg/day (a)	£0.0172	£1.72	BNF 62
Methotrexate (2.5 mg)	Titrated up to 15 mg/week (b)	£0.0467	£0.12	BNF 62
Adalimumab (40 mg)	80 mg loading dose followed by 40 mg every other week	£8.80	£352.14	BNF 62
Etanercept (50 mg)	50 mg/week	£3.58	£178.75	BNF 62
Infliximab (100 mg)	5 mg/kg at weeks 0, 2, 6 then every 8 weeks (c)	£4.20	£419.62	BNF 62
Ustekinumab (45 mg)	45 mg at weeks 0, 4 and then every 12 weeks	£47.71	£2147.00	BNF 62

(a) Based on 75 kg patient receiving 4 mg/kg/day
(b) Titrated up weekly from 2.5 mg
(c) Based on 80 kg patient receiving 5 mg/kg/infusion or 4 x 100 mg vials per infusion generally

'Trial' period

Previous NICE guidance has stipulated that biologic therapies should be trialled for a given number of weeks and discontinued if an adequate response has not been observed. The recommended trial period varies between drugs: 12 weeks for etanercept, 10 weeks for infliximab and 16 weeks for both adalimumab and ustekinumab. Because we were not modelling specific biologic therapies, but rather an average biologic, we took the mean of these different trial lengths: 13.5 weeks. Based on the dosing schedule in Table 4, a 13.5 week trial period does not affect the costs for drugs like infliximab and ustekinumab, however it might overestimate the costs for etanercept slightly and underestimate costs for adalimumab. Similarly, using a 13.5 week trial period may underestimate benefits for drugs such as adalimumab and ustekinumab as non-responding patients are forced to stop slightly earlier, but it will overestimate benefits for drugs such as infliximab and etanercept as it

would mean that patients who should have stopped will continue to accrue benefits. Overall, the GDG expects the costs and benefits to even out reasonably using an average 13.5 week trial period.

In addition to the cost of the biologic agents themselves, the trial period includes costs of administration, monitoring and outpatient visits. Only infliximab was associated with additional administration costs, which amounted to a regular day/night admission for an infusion (JD02C: £316)[70]. Monitoring tests include full blood count, liver function test and urea and electrolytes (which includes serum creatinine testing). The frequencies and unit costs of each of these monitoring tests for each biologic agent are presented in Table 45. The unit costs of each of these monitoring tests were taken from Woolacott and colleagues and inflated to 2011, using the PSSRU inflation index[69]. The number of outpatient visits during the trial period for each biologic agent is also presented in Table 45.

Table 45: Quantity of monitoring tests and outpatient visits during 13.5 week trial period

Biologic	FBC (£2.83)	LFT (£0.71)	U&E (£1.31)	Outpatient visits (£82)
Adalimumab	2	2	2	2
Etanercept	2	2	2	2
Infliximab	3	3	3	1 (a)
Ustekinumab	2	2	2	2

(a) Patients are reviewed during infusion visits and then one additional outpatient appointment.
FBC, Full blood count; LFT, liver function test; U&E, Urea and Electrolytes, including serum creatinine

Based on the resource use and unit costs presented in Table 44 and Table 45, the total 13.5-week trial period cost for each biologic agent is presented in Table 46. The un-weighted average across all biologics for the 'trial' period is £4,031.

Table 46: Total trial period cost of each biologic therapy and average across all biologic therapies

Drug	Total drug costs	Total administration costs	Total monitoring costs	Total outpatient costs	Total Cost
Adalimumab	£2,817		£9.70	£164	£2,991
Etanercept	£2,413		£9.70	£164	£2,587
Infliximab	£5,035	£947	£14.55	£82	£6,079
Ustekinumab	£4,294		£9.70	£164	£4,468
Average biologic agent					**£4,031**

The frequency of use of different biologics was obtained from the British Association of Dermatologists Biologic Interventions Register (cut-off 31st March 2012): Adalimumab= 1225, Etanercept = 665, Infliximab =143, Ustekinumab= 451 (Personal communication Dr Nicola Lawes 18th April 2012). These were used to estimate a weighted average biologic cost of £3,329, which was used in a sensitivity analysis. These weights were not used in the base case analysis, since they reflect any use of a biologic, which is likely to be quite different to the distribution of 2nd-line biologics.

'Treatment' period

Estimates of resource use and costs were quantified for annual cycles and include the same items (drugs, administration and monitoring) as those outlined in the previous section. In addition to the biologic agents, we have presented the annual cost of treatment with methotrexate and ciclosporin, two drugs included as part of best supportive care.

Table 47: Annual drug costs

Biologic	Dose	Notes/Assumption	Unit Cost	Total Cost
Methotrexate	15 mg per week		£0.05 per mg	£36
Ciclosporin	300 mg per day	Max 2 years	0.02 per mg	£1,880
Adalimumab	40 mg every two weeks		£352.14 per 40 mg	£9,156
Etanercept	50 mg once weekly		£178.75 per 50 mg	£9,295
Infliximab	5 mg/kg every 8 weeks	4 x 100 mg vials per infusion	£419.62 per 100 mg	£10,910
Ustekinumab	45 mg every 12 weeks		£2,147 per 45 mg	£9,304

Monitoring for patients continuing biologic therapy during the treatment period is assumed to be less frequent as are follow-up outpatient visits, taking place only once every 3 months. Monitoring of patients undergoing treatment with methotrexate is assumed to include the additional costs of 3-monthly PIIINP testing and the infrequent, but occasional liver biopsy. The annual rate of 0.04 biopsies per year was taken from Chalmers and colleagues[86], a study that was included in the health economic review for methotrexate monitoring (see chapter 19). Patients being treated with ciclosporin are also assumed to undergo glomerular filtration rate testing once per year. Annual frequencies and unit costs of these monitoring tests for each biologic agent and both conventional systemic therapies are presented in Table 48. Costs for glomerular filtration rate (GFR) testing and liver biopsy were taken from NHS reference costs. Liver biopsy was assumed to be performed as a day case procedure (code GB04Z) and GFR testing was based on a weighted average of the test performed as a diagnostic imaging outpatient procedure, direct access procedure or other (code RA37Z). The number of outpatient visits during the trial period for each biologic agent is also presented.

Table 48: Number of annual monitoring tests and outpatient visits

Biologic	FBC (£2.83)	LFT (£0.71)	U&E (£1.31)	PIIINP (£25.29)	GFR (£233)	Liver biopsy (£553)	Outpatient visit (£82)
Methotrexate	4	4	4	4		0.04 (a)	4
Ciclosporin	4	4	4		1		4
Adalimumab	4	4	4				4
Etanercept	4	4	4				4
Infliximab	4	4	4				4
Ustekinumab	4	4	4				4

(a) Frequency of liver biopsy with methotrexate with concurrent use of PIIINP test was based on estimates from Chalmers and colleagues[86]
(b) GFR, Glomerular Filtration Rate

Based on the resource use and unit costs presented in Table 47 and Table 48, the total annual treatment period cost for each biologic agent, ciclosporin and methotrexate is presented in Table 49. The un-weighted average annual cost across all biologics for the 'treatment period' is £10,527. A weighted average of £9,787, calculated in the same manner as for the 'trial period' was used in a sensitivity analysis.

Table 49: Total annual 'treatment' period costs

Biologic	Total drug costs (see Table 47)	Total administration costs (see Table 47)	Total monitoring cost (see Table 48)	Total outpatient costs (see Table 48)	Total Cost
Methotrexate	£36		£143	£328	£507
Ciclosporin	£1,880		£253	£328	£2,461

Biologic	Total drug costs (see Table 47)	Total administration costs (see Table 47)	Total monitoring cost (see Table 48)	Total outpatient costs (see Table 48)	Total Cost
Adalimumab	£2,817		£19.40	£328	£9,503
Etanercept	£2,413		£19.40	£328	£9,643
Infliximab	£5,035	£2,052	£19.40	£328	£13,310
Ustekinumab	£4,294		£19.40	£328	£9,651
Average biologic agent					**£10,527**

Best supportive care

Based on discussions with the GDG, evidence from two retrospective cohort studies and assumptions made in previous NICE technology appraisals, the following definition for best supportive care was used in the NCGC model. For details about the evidence and discussions feeding into this definition, see Appendix P. The summary presented here is broken up into different resource categories and then summarised at the end in a single table (Table 50). Resource use and costing estimates for outpatient attendances, monitoring and laboratory testing for ciclosporin and methotrexate are presented in the previous sections.

Drug and other treatments

There is recognition that at the point at which patients become eligible for a first biologic therapy, they must have exhausted treatment options such as conventional systemic therapy and phototherapy, including PUVA. The GDG considered that although these therapies had either proved ineffective or given rise to certain toxicities, the patients for whom a second biologic was being considered were unlikely to go without treatment altogether. In the absence of a second biologic therapy, the likelihood is that they would be cycled through different modalities, accepting the associated risks. On this basis, the NCGC model has attempted to approach the treatments comprising 'best supportive care' in a pragmatic fashion, albeit with limitations.

Drugs included under 'best supportive care' (BSC) and the proportions of patients receiving each were defined by the GDG in the following way:

- 45% of patients will be managed with ciclosporin for a maximum of 2 years
- 45% of patients will be managed with methotrexate for the entire time horizon
- 10% will be managed with no active pharmacological treatment (some patients will opt for no treatment given the possible risks associated with conventional systemic therapies)

These proportions were varied in sensitivity and scenario analyses.

Phototherapy and day care attendances

We have assumed that 16% of patients will undergo one course of narrowband UVB each year (24 sessions). This is based on the estimated use of PUVA in the Driessen study[87] during the year prior to initiation of biologic therapy. Given the high probability of contraindication to PUVA in the hypothetical population of the NCGC model, a course of narrowband UVB was thought to be more realistic than further PUVA.

The GDG indicated that if the service is available, the population included in the NCGC model (failed biologic therapy) is very likely to utilise day care centre services for intensive, supervised topical or

combination therapies. On this basis, the NCGC model has assumed that all patients receiving BSC will attend a day centre for specialist applied topicals or other specialist treatment 5 times per year.

Inpatient admissions and length of stay

For details on how resource use estimates for inpatient stays were derived, see Appendix P: section P.5.2.5.

Patients receiving BSC were assumed to be stratified into two groups based on a recent Dutch cohort study[87]: 82% high-need and 18% very high-need. In the base case, it was assumed that high-need patients will require one hospital admission per year, which was assumed to correspond to a mean length of stay of 20.8 days (based on data from Woods and colleagues[88]). It was assumed that very high-need patients (18%) will require 2.55 hospital admissions per year, each also 20.8 days in length. The weighted average number of inpatient days per year is thus 26.6 days.

Given that these variables are quite uncertain, extensive sensitivity analyses were performed to explore how small and large changes in resource use might affect the cost-effectiveness of second line biologic therapy. In particular, the proportions of high- and very-high need patients and the number of annual admissions and mean length of stay per group were varied.

Summary of best supportive care

The working definition of best supportive care, in the context of patients with moderate to very severe plaque psoriasis who are being considered for further biologic therapy, is summarised in terms of resource use in Table 50. This is based on several different sources of information and supplemented by GDG experience and opinion. This defined package of services is expected to cost an annual £10,731. Due to substantial uncertainties in these model parameters, they were subject to extensive sensitivity analyses, each of which was considered by the GDG as they looked to make guideline recommendations that would represent an effective and cost-effective use of NHS resources.

Table 50: Assumed resource use for best supportive care

	Total annual cost			
Component	**Proportion receiving**	**Resource use components**		**Total Cost**
Drugs				
Methotrexate	45% (a)			£228
Ciclosporin (b)	45% (a)			£1,107
No drug	10% (a)	5 OP visits		£41
Other treatment				
Day centre care	100% (a)	5 visits		£1,813
NBUVB	16% (c)	1 course	24 sessions	£327
Inpatient care (g)				
High need	82% (d)	1 admission (a)	20.8 days per admission (f)	£4,625
Very high need	18% (d)	2.55 admissions (e)		£2,589
TOTAL				**£10,730 (h)**

(a) Based on GDG opinion
(b) Maximum treatment 2 years; after 2 years then no drug
(c) Based on proportion receiving PUVA in year before starting biological therapy in Driessen and colleagues[87]
(d) Based on split in Driessen and colleagues[87] (under/over 30 days in hospital per annum)
(e) Calculated based on mean length of stay from Woods[88] (20.8) and mean in hospital days per annum in the very high need group in Driessen[87] (53.0).

(f) Based on mean length of stay for patients admitted with baseline PASI 10 to 20 in Woods[88]. 23.7 days used in sensitivity analysis.

(g) Weighted average length of stay equals 26.6 days per year per patient (20.8[0.82*1+0.18*2.55]=26.6) and weighted average cost equals £7,214 per patient.*

(h) Note: previous TAs[79-82] have estimated this cost to be approximately £5,327.71 (21 days in hospital + 2 outpatient visits per annum)

O.2.4 Computations

The model was constructed in TreeAge Pro 2009 and was evaluated by cohort simulation. All hypothetical patients start treatment with a biologic therapy and achieve a different level of PASI response, with >PASI75 classified as responding and <PASI75 classified as not responding. Only responders are assumed to continue treatment and can subsequently drop out and move on to best supportive care. Each annual cycle the cohort spends in a given health state is counted.

Total QALYs were calculated from the above information as follows. Each annual cycle, the time spent in each health state of the model was weighted by the utility for that state. The QALYs per cycle were then discounted to reflect time preference. QALYs during year one were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle. The QALYs that were accrued during the initial 13.5 week trial period were added to the QALYs accrued in the first cycle.

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

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

Total costs were calculated from the above information as follows. Each cycle, the time spent in each state of the model was multiplied by the costs for that state. The costs per cycle were then discounted to reflect time preference. Costs during year one were not discounted. The total discounted costs were the sum of the discounted costs per cycle. The costs that were accrued during the initial 13.5 week trial period were added to the costs accrued in the first cycle.

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

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

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

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

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

ICERs were calculated based on mean costs and effects as estimated during the probabilistic implementation of the model. Results are presented on the cost-effectiveness plane where the total cost and total QALYs are plotted for both treatment options. Best supportive care is located at the

origin, defined as the intersection between its total QALYs (on the x-axis) and total cost (on the y-axis). The slope of the line connecting best supportive care to biologic therapy is equal to the incremental cost-effectiveness ratio, the value of which is labelled.

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

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

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

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

O.2.5 Sensitivity analyses

A series of one-way sensitivity analyses and scenario analyses were performed to assess how changes in one or more parameters or assumptions might change the conclusions of the analysis. In the first series, we focused on inputs relating to the costs and effectiveness of biologic therapies. In the second set of sensitivity analyses, we explored how changes in the sources for health state utilities might impact the conclusions of the analysis. The third set of scenarios explored how changes in the effectiveness of best supportive care might alter the conclusions arising from the base case. Finally, an extensive set of scenario analyses was performed to explore how variation in the assumed resource use of best supportive care might impact the relative cost-effectiveness of the strategies. The results of the sensitivity analysis were interpreted alongside the base case results such that the GDG was aware of the key drivers of cost-effectiveness and uncertainty.

O.2.6 Model validation

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

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

O.3 Results

O.3.1 Base case

Results of the base case suggest that compared to best supportive care, a second line biologic therapy is likely to be cost effective at a willingness to pay threshold of £20,000 per QALY gained. Results of the incremental analysis are presented in Table 51 and in Figure 356. Total costs disaggregated by type of resource use are presented in Table 52.

Table 51: Incremental analysis of base case results

Strategy	Total Costs	Incremental Cost	Total Benefit (QALYs)	Incremental Benefit (QALYs)	ICER (£/QALY)
BSC	£87,155		0.478		

Strategy	Total Costs	Incremental Cost	Total Benefit (QALYs)	Incremental Benefit (QALYs)	ICER (£/QALY)
Biologic	£90,661	£3,506	0.804	0.326	£10,755

Figure 356: Base case results on the cost-effectiveness plane

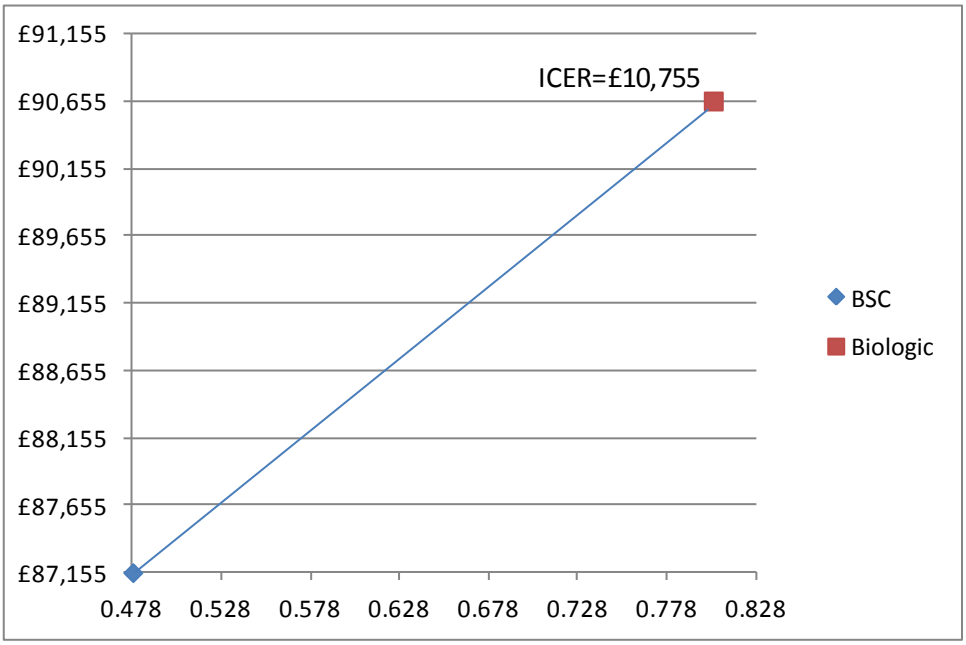


Table 52: Breakdown of costs

Sensitivity analysis	Biologic	BSC
Drug costs	£25,518	£1,603
Outpatient costs	£3,124	£3,192
Inpatient costs	£46,263	£62,916
Monitoring costs	£727	£756
Administration costs	£1,289	£0
NB-UVB	£2,104	£2,861
Day centre visits	£11,626	£15,811
TOTAL	**£90,650**	**£87,139**

Note: Totals reported here may differ slightly from those reported in Table 51, as costs for each category of resource use were estimated as part of a separate run of the probabilistic analysis and variation in the sampled values may give rise to slight differences.

Results indicate that switching to a second biologic following intolerance to or failure of a first biologic is likely to cost £3,506 more over 10 years than switching to best supportive care, but this cost is likely to be offset by a 0.326 gain in QALYs. The incremental cost-effectiveness ratio (ICER) of second biologic compared to best supportive care is £10,755 per QALY, a value well below the NICE willingness to pay threshold range of £20,000 to £30,000 per QALY gained.

Table 53: Total and incremental costs, benefits and net monetary benefits from PSA

	Biologic therapy (95% CI)	BSC (95% CI)	Incrementals (95% CI) Biologic vs BSC
Total cost (£)	90,661	87,155	3,506

	Biologic therapy (95% CI)	BSC (95% CI)	Incrementals (95% CI) Biologic vs BSC
	(88,246 to 93,171)	(83,920 to 90,533)	(-617 to 1,687)
Total benefit (QALYs)	0.804 (0.517 to 1.291)	0.478 (0.323 to 0.665)	0.326 (-0.097 to 0.749)
NMB at £20k threshold (£)	-74,571 (-80,918 to -64,733)	-77,600 (-82,210 to -72,729)	3,029 (-6,350 to 12,408)
NMB at £30k threshold (£)	-66,526 (-75,475 to -51,888)	-72,823 (-78,584 to -66,321)	6,297 (-6,995 to 19,589)

O.3.2 Sensitivity analyses

A series of one-way sensitivity analyses were performed to explore how changes in key variables might affect the base case results.

Table 54: Results of sensitivity analyses around biologic inputs

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
Infliximab only	£34,212	7%	27%
Etanercept only	£782	100%	100%
Adalimumab only	£1,134	100%	100%
Ustekinumab only	£6,536	98%	100%
Infliximab and Ustekinumab only	£20,338	36%	75%
Weighted average biologics (15% Infliximab)	£7,497	97%	100%
Weighted average biologics (BADBIR data)	4,543	100%	100%
Continue treatment if PASI50	£9,703	93%	99%
10% annual drop out	£7,760	97%	100%
30% annual drop out	£14,123	72%	93%
50% annual drop out	£21,881	31%	69%

Under base case assumptions, switching to a second biologic is likely to be cost-effective (£10,730 per QALY compared to best supportive care). Considerable uncertainty is revealed when assumptions about biologics are varied (Table 54).

- If highest cost biologic is assumed (Infliximab), a second biologic is less likely to be cost-effective given a £30k threshold (27% probability of being cost-effective).
- If lowest cost biologics are assumed, a second biologic is almost certainly cost-effective compared to best supportive care.
- If only infliximab and ustekinumab are included (i.e. etanercept and adalimumab are not options), then the ICER increases to £20,338 per QALY, but is still potentially cost-effective at a willingness to pay threshold of £30,000 per QALY.

Second line biologic becomes slightly more cost-effective if patients are allowed to continue with a PASI50 response and conclusions are not very sensitive to plausible estimates of annual drop out rate.

Table 55: Results of sensitivity analyses around utility inputs

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
No utility gain for BSC PASI00	£10,637	89%	98%
4th Quartile DLQI at baseline	£5,864	99%	100%
Adalimumab STA utilities	£8,041	100%	100%
Ustekinumab STA utilities	£8,655	100%	100%
Ustekinumab STA utilities (SF-36)	£25,048	14%	79%

Results of sensitivity analyses around utility inputs presented in Table 55 show that base case results are relatively insensitive to changes in the source of quality of life estimates.

- It appears that biologics become more cost-effective using utility values for patients with the worst DLQI at baseline, an unsurprising result given that these are the patients with the most to gain from successful treatment.
- The cost-effectiveness of second line biologic therapy diminishes when using utility estimates derived from SF-36, which were included in the ustekinumab single technology appraisal; however, even using these estimates a second biologic has a 79% probability of being cost-effective at a threshold of £30,000 per QALY.

Table 56: Results of sensitivity analyses around response rates for best supportive care

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**
Placebo response from trials	£10,451	90%	99%
65% response rate (Woods 2008)	£22,411	24%	48%
83% response rate (Woods 2008)	£31,892	16%	24%

Results are very sensitive to changes in estimates of effect for best supportive care (Table 56).

- When best supportive care is assumed to offer no benefits at all (i.e. 0% of patients are assumed to achieve ≥PASI50), biologics are very slightly more cost-effective than in the base case.
- When response rates for inpatient admission observed in Woods 2008 are used, uncertainty in the cost-effectiveness of second line biologic therapy increases.
  - If inpatient care produces a PASI50 response rate of 65%, second line biologic is cost-effective in fewer than 50% of simulations at a £30k threshold
  - If inpatient care produces a PASI50 response rate of 83%, the probability of switching to a second line biologic therapy being cost-effective goes down to 24% (in other words, best supportive care has a 76% probability of being more cost-effective than second biologic).

Table 57: Results of sensitivity analyses around resource use inputs for best supportive care

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
Base Case	**£10,730**	**88%**	**98%**

Sensitivity analysis	ICER Biologic vs BSC	Probability of being cost-effective at £20k/QALY	Probability of being cost-effective at £30k/QALY
No drugs in BSC	£9,307	93%	99%
Longer length of stay (23.7 days)	£5,137	100%	100%
30% very high need	£3,306	100%	100%
5% very high need	£18,694	45%	81%
0.25 hospitalisations for high need and 2.55 hospitalisations for very high need (match Driessen 2010)	£35,079	7%	25%
0.5 hospitalisations for high need and 2 hospitalisations for very high need	£30,944	10%	35%
1 hospitalisation for all	£21,926	30%	69%
0.312 hospitalisations for all (match Fonia 2010)	£49,575	2%	8%
No hospitalisations	£60,998	1%	5%
1 hospitalisation for all and no drugs	£20,369	37%	75%
1 hospitalisation and 5 outpatient visits per year	£35,259	7%	25%
1 hospitalisation and 5 outpatient visits per year and 4th Quartile DLQI	£19,391	43%	77%

Results are very sensitive to changes in estimates of resource use assumed for best supportive care (Table 57). The cost-effectiveness of switching to a second biologic improves if mean length of stay per admission increases and if a greater proportion of patients are classified as very high need (thus requiring more inpatient admissions per year).

The likelihood of switching to a second biologic being cost-effective decreases if

- The proportion of very high need patients decreases
- The number of hospitalisations decreases
- The other types of care in best supportive care are removed (i.e. no UVB, no day centre, no drugs)

It is worth highlighting two scenarios in particular:

- In Driessen 2010[87], the mean number of inpatient days for patients who had less than 30 days per annum was 5.1 and the mean number of inpatient days for patients who had more than 30 days per annum was 53.0. The weighted average length of stay was thus 13.722 inpatient days per annum. When this was recreated in the model, the ICER for biologic therapy compared to best supportive care when up to £35,079 and had a 25% probability of being cost-effective at £30k per QALY.
- In Fonia 2010[89], the mean number of inpatient days for all patients was 6.49. When this was recreated in the model, the ICER for biologic therapy compared to best supportive care when up to £49,575 and had an 8% probability of being cost-effective at £30k per QALY.

These studies estimated mean inpatient days in the year preceding initial treatment with biologic therapy and thus the values may underestimate the likely resource use in the minority of patients represented in this model, who are likely to be sicker since they have already failed one line of biologic treatment.

O.4 Discussion

O.4.1 Summary of results

In assessing the cost-effectiveness of biological therapy in patients with moderate to severe psoriasis who have previously been treated with biological therapy, no information was available from the published economic literature. It was therefore considered a priority to undertake original evaluation for the guideline in order to inform guideline recommendations. This analysis suggests that switching to a second line biological drug is potentially cost-effective compared to a strategy of best supportive care without biological therapy. Uncertainties in the analysis were explored through extensive sensitivity analysis which changed the conclusion in some cases, namely those in which best supportive care was assumed to produce some clinical and quality of life improvements or was assumed to be less resource intensive in terms of inpatient stays and other forms of hospital-based care (e.g. UVB, day centre treatments).

O.4.2 Limitations

Most parameters in the model are highly uncertain which makes the analysis quite exploratory and interpretation a challenge. The clinical evidence for biological treatments evaluated in this population is limited, although it clearly shows there to be a benefit compared to placebo. However, in reality, this population would never receive simply a placebo. In the absence of biological therapy, they would likely receive a package of care with multiple components which may or may not produce quality of life benefits. Defining this package of care was a significant challenge, and the analysis relied on a mixture of evidence from recent cost analyses and GDG opinion. Indeed, efficacy and resource use associated with best supportive care in the absence of biologic therapy were among the most significant drivers of uncertainty in the analysis.

In terms of the population, the clinical evidence is quite muddled with no distinctions between patients who were primary or secondary treatment failures, intolerant to treatment or simply switched as part of a clinical trial. There is also uncertainty as to whether these patients have more, less or equally severe psoriasis as patients who are naïve to biological therapy. The GDG considered it likely that this group would have more severe, treatment-resistant disease and would thus represent a very resource-intensive group as well as one with a great deal to gain in terms of quality of life if treatment was successful.

As has been outlined in previous appraisals of biological therapy, there is relatively limited long-term experience with biological therapies, and thus estimates of drop out and sustained remission are based on assumptions. There was also limited data on adverse events, both in terms of their incidence as well as their impact on resource use and quality of life. These were excluded from the NCGC analysis, but the GDG did not think that this would change conclusions.

O.4.3 Interpretation of the evidence

There was no economic evidence from the published literature to inform the GDG on the cost-effectiveness of offering a second biological drug to patients with moderate to severe psoriasis who have not responded to, lost response to or been intolerant to a first biological drug. Original decision modelling undertaken for the guideline showed that switching to a second biological drug may be more cost-effective than moving to best supportive care without biological therapy, but there was substantial uncertainty surrounding this conclusion. Uncertainty was driven by unknowns regarding the definition and efficacy of best supportive care.

The GDG considered definitions of best supportive care from previous economic analyses in the UK and found that the defined resource use was likely to be a gross underestimate. Based on the NICE eligibility criteria for biological therapy, these patients will have failed to respond to or will have been

intolerant to conventional systemic therapies (methotrexate and ciclosporin) thus limiting their further management options dramatically. In the absence of these relatively inexpensive treatment options, the GDG considered that the majority of these patients would rely on costly outpatient day care and very costly inpatient care to manage their disease. Based on recent resource utilisation studies from the UK and Netherlands and supported by their clinical experience, they outlined a much more resource intensive package of services likely to be used or required by people with moderate to severe psoriasis who did not have access to biological therapy.

The GDG considered the results of the extensive sensitivity analyses around the cost of best supportive care. They considered that when best supportive care was less resource intensive (i.e. fewer annual hospitalisations, shorter length of stay and/or less outpatient day care),switching to a second biological drug was less likely to represent better value for NHS resources. Results showed that only when patients were assumed to have the worst baseline quality of life (and hence have the most to gain from successful treatment) would the substantial additional cost of delivering biological therapy compared to a less resource intensive best supportive care be offset. Conversely, if best supportive care was assumed to be more resource intensive than in the base case, then biological therapy was very likely to be most cost-effective, regardless of baseline quality of life.

There was also uncertainty in the effectiveness of this newly defined best supportive care. Previous analyses have used the placebo response rates from the randomised controlled trials, which when used in the guideline model was virtually equivalent to assuming no response at all. This was varied upwards based on observational data from the UK which showed that response to inpatient treatment ranged between 65% and 83%. When inpatient treatment was assumed to be as effective as this, then the incremental cost-effectiveness ratio of switching to an alternative biological therapy increased to between £20,000 and £30,000 per QALY gained. Although quality of life gains are generally attached only to the clinical outcomes (i.e. PASI response), the GDG discussed whether gains might be affected by how the outcome was reached. They considered that although 3 weeks in hospital may induce an adequate level of response (PASI50), this could have a substantial negative impact on a patient's quality of life compared to a once or twice weekly injection or even an infusion every few months. Furthermore, in order to maintain that level of response, patients would likely have to carry on with regular outpatient day care appointments or use drug treatments that have failed in the past or have potentially serious adverse events (e.g. renal impairment or hepatotoxicity).

The GDG recognised that the model included a population of patients with variable reasons for undergoing treatment with a second biological drug. This includes patients who may have been primary or secondary non-responders, patients who may have been intolerant to an initial biological or other reasons unrelated to the initial treatment. There is also no information about what biological therapy or therapies to which they may have been exposed. It is also unclear as to whether these patients have more or less severe disease than in trials of patients naïve to biological therapy. The GDG considered whether any of these patient differences were likely to impact the cost-effectiveness of biological therapy over best supportive care, and they concluded that the benefit over placebo was likely to be significant enough in any of these groups to justify the additional cost of biological therapy. This was especially true if the patient had very severe disease, as this group would have the most to gain from successful treatment. They noted too that the population likely to reach this point in the care pathway is very small (fewer than 1000 patients). They decided that switching to a second biological drug should be considered in all patients following failure of a first biological drug and noted that the same criteria as outlined in previous NICE guidance should be used to determine eligibility.

O.4.4 Conclusion

New economic analysis from a current UK NHS and PSS perspective comparing biologic therapy to best supportive care found that further biologic therapy is likely to offer better value for NHS resources in the treatment of patients with moderate to severe plaque psoriasis who have previously

been exposed to biologic therapy and either failed to respond, lost response or were intolerant to this initial biologic therapy. There is substantial uncertainty in this conclusion, which was explored through extensive sensitivity analyses around various parameters.

- Sensitivity analyses in which the cost of biologic therapy was assumed to be very high (e.g. the cost of infliximab) found that switching to an alternative biologic therapy was unlikely to be cost effective compared to best supportive care.
- Sensitivity analyses in which the cost of best supportive care was assumed to be lower than in the base case (due to fewer very high need patients, fewer hospitalisations, shorter length of stay or fewer visits to day care centre) or when it was more effective than in the base case found that switching to an alternative biologic therapy was unlikely to be cost effective compared to best supportive care.
- Sensitivity analysis in which patients were assumed to start treatment with the worst baseline quality of life, and therefore had the most to gain from successful treatment, found that further biologic therapy was likely to be more cost effective even when resource use for best supportive care was assumed to be low.

Appendix P: Review of resource use and cost data to use in defining 'best supportive care' for NCGC economic model

P.1 Introduction

This appendix is a review of resource use and cost data available in the published literature, which was used to estimate suitable parameters with which to populate the best supportive care arm of the NCGC model. For the purposes of this model the GDG sought to define 'best supportive care' (BSC) in terms of NHS resource use for the average patient for whom a second biologic is being considered.

The review has been structured to provide first a brief summary of assumptions about BSC that have been made in previous NICE guidance on biologic therapies in the treatment of moderate to severe psoriasis. Next, the review looks to recently published resource use studies of high-need psoriasis patients in the year before and the year of initiation of biologic therapy. Thirdly, some of the issues raised by the GDG in considering the evidence and population are highlighted. Finally, everything is brought together to provide a working definition of BSC to be used in the NCGC model.

P.2 Definition in technology appraisals

Woolacott and colleagues[84], authors of the original health technology appraisal of biologic therapy used in the treatment of psoriasis, were the first to define BSC in psoriasis. They used placebo response rates from the placebo-controlled trials of systemic and biologic therapies in order to define the benefits of BSC and used expert opinion to inform likely resources used. All subsequent technology appraisals appear to have used the same or very similar definitions for BSC.

The authors assumed that there were no significant additional treatment costs associated with BSC compared to older systemic treatments (methotrexate and ciclosporin). It was assumed that patients on BSC would have two outpatient visits annually. The cost of an outpatient appointment was based on the NHS Reference Cost category J10op ('Major dermatological conditions; other attendance without other investigation or procedure) and was £56.60[90].

The main additional cost with BSC in the model resulted from increased rate of hospitalisation due to a lower rate of PASI75 response. No published data were available to inform the rate of hospitalisation so estimates were based on a range of scenarios informed by expert opinion.

Length of stay for an inpatient hospital admission was based on Department of Health Hospital Episode Statistics (2002-03)[91] for psoriasis which gave a mean of 19.6 days. This statistic was supported by evidence from recent audits of two local hospitals (supplied to the authors from personal communication) which had an average length of stay of 22.3 and 22.7 days. In key scenario analyses, the authors assumed that patients would spend an average of 21 days in hospital per year. The cost of an inpatient day was based on the average of two NHS Reference Cost categories: elective inpatient J39 ('major dermatological conditions (>69 or w cc: aged over 69 or with co-morbidities or complications)') and J40 ('major dermatological conditions (<70 or w/o cc)'). Using the number of Finished Consultant Episodes to weight the costs, the resulting weighted average cost for an inpatient day was £248.31. Thus, the total annual cost for inpatient stays was £5,214.51.

The GDG discussed using a similar definition of BSC (i.e. 2 outpatient visits in a base case and 21 inpatient days per year in a scenario analysis), but argued that these estimates of resource use are likely to be an underestimate of what currently happens in clinical practice. They believed that the

patients meeting the eligibility criteria for biologic therapy are generally high-need patients and utilise a lot of health care resources through inpatient admissions, lengthy hospital stays, frequent visits to day clinics for specialist-applied topical treatments and UVB and monitoring toxicity related to systemic treatments. Based on the GDG experience, the group of patients modelled by Woolacott and colleagues would receive 'no treatment' only very rarely and would almost certainly require more care than 2 outpatient visits per year and likely more than 21 days in hospital.

When translating this information to build the NCGC model, which focuses on patients who are being considered for treatment with a second biologic, the GDG is certain that these resource use estimates are inadequate. In their opinion, the group of patients requiring a second biologic are likely to be even more high-need and resource intensive; therefore it would be inappropriate to assume the same assumptions about what comprises BSC.

P.3 Cohort studies of resource use

Two cohort studies have been published in response to a request for more research on the actual resource use of high-need psoriasis patients. One study[89] was undertaken at a tertiary dermatology unit in the UK and the other study[87] was undertaken at a tertiary dermatology unit in the Netherlands.

P.3.1 Fonia and colleagues 2011[89]

Fonia and colleagues investigated resource use in a cohort of 76 patients with severe psoriasis before and after the introduction of biologic therapy at St John's Institute of Dermatology. The primary objective of the retrospective observational study was to compare resource use and associated costs in patients with plaque psoriasis for a period of 12 months before and for up to 12 months immediately after starting biologic therapy. They also captured estimates of quality of life and disease severity during these before and after periods. Costs were estimated from an NHS perspective and used 2008 British pounds.

The relative proportions of patients on each biologic were:

- 7.9% on adalimumab
- 11.8% on efalizumab
- 71% on etanercept
- 31.6% on infliximab.

The pattern of biologic drug use observed reflects the availability of each drug during the time period of data collection (2003-08). Their data also indicate that in general etanercept is used continuously, rather than intermittently.

Patients were on a variety of conventional systemic drugs prior to initiation of biologic therapy: 47% were taking ciclosporin; 41% were taking methotrexate; 25% were taking fumarates; 24% were taking acitretin. Upon starting biologic therapy, half of people taking ciclosporin stopped taking it; all but one patient stopped taking acitretin; all but 3 patients stopped taking fumarates. The number of patients taking methotrexate reduced very slightly (31 to 27 patients) and the mean number of days on methotrexate reduced very slightly as well (104.3 days to 100.2 days).

Inpatient admissions were less frequent after initiation of biologic therapy (absolute values not reported) and length of stay was reduced (6.49 days to 1.55 days). There was no difference in outpatient attendances (3.22 vs 3.25 visits). Day ward admissions were more frequent upon initiation of biologic therapy (0.14 vs 1.16) with 91% attributable to infusion of infliximab.

Overall, mean hospital costs decreased by £1,682 in the year following initiation of biologic therapy. However, these savings are counterbalanced by the increase in drug costs, which amounted to £9,456. In the end, there was a significant increase in mean cost per patient of £7,774 in the period after biologic therapy was initiated.

The authors note that following initiation with biologic therapy, the mean PASI score fell by 8.9 points, from 18.7 to 9.8 which represents a mean PASI improvement of 48%. They point out that 'while the degree of improvement was less than that reported in randomised controlled trials, this may reflect a relatively treatment resistant group (failed prior systemic therapy) and/or differences between real life and highly controlled clinical trial settings.' They also highlight the fact that many patients will have switched to biologic from ciclosporin and/or methotrexate due to toxicities rather than to poor disease control, therefore improvement in PASI for these patients might not be reflected.

P.3.2 Driessen and colleagues 2011[87]

The authors investigated resource use in a cohort of 67 patients with severe psoriasis before and after the introduction of biologic therapy at Radbound University Nijmegen Medical Centre Department of Dermatology between February 2005 and February 2009. The objective of the retrospective cohort analysis was to compare resource use and associated costs in patients with plaque psoriasis for a period of 12 months before and for up to 12 months after starting initial biologic therapy.

The relative proportions of patients on each biologic were:

- 18% on adalimumab (18% at time of analysis)
- 30% on efalizumab (9% at time of analysis)
- 95% on etanercept (72% at time of analysis)
- 6% on infliximab (1% at time of analysis)

The pattern of biologic drug use observed reflects the availability of each drug during the time period of data collection (2005-09). 63% were treated with only one biologic (majority etanercept), 28% were treated with two biologics and 9% were treated with three or four biologics. The GDG believes that it is extremely improbable that a patient in the UK would be managed on any more than a single biologic at a time.

Patients were on a variety of conventional systemic drugs prior to initiation of biologic therapy: 85% were taking methotrexate; 51% were taking ciclosporin; 51% were taking acitretin; 37% were taking fumarates; 16% undergoing PUVA. Upon starting biologic therapy, three-quarters of people taking methotrexate, ciclosporin, acitretin and fumarates stopped taking them.

The authors separated the analysis of resource use by mean length of inpatient stay asserting that the yearly expenses for biologic treatment equals that of 30 hospital admission days. Therefore, they analysed resource use and costs for patients with mean length of stay less than 30 days and mean length of stay more than 30 days separately.

For the group with a mean length of stay less than 30 days (82% of the cohort), the number of days spent in day care per year reduced from 5.1 to 0.3 upon initiation of biologic therapy. Mean hospital inpatient days per year were reduced from and 14.9 to 5.4 days. There was little change in the mean number of outpatient consultations between the two periods (7.6 vs 7.0 visits). In this group, mean hospital costs (inpatient and day care) decreased by €5,621 in the year following initiation of biologic therapy. However, these savings in hospital costs are counterbalanced by the increase in drug costs, which amounted to €13,325. Looking at overall costs in this group, there was a significant increase in mean cost per patient of approximately €7,500 in the period after biologic therapy was initiated.

For the group with a mean length of stay longer than 30 days (18% of the cohort), the median inpatient length of stay was 53 days in the pre-biologic treatment period and 5.3 days upon introduction of biologic therapy.

In the overall patient group, the mean PASI at the start of biologic treatment was 19.0 and during treatment this decreased to 6.4, indicating a mean improvement of 66.4%. 73% of patients reached a PASI50 and 43% achieved a PASI75.

One key limitation of the analysis is that only patients that finished 12 months of biologic therapy were included; therefore, there are no estimates of resource use for patients who did not respond or were intolerant to biologic therapy.

P.3.3 Woods and colleagues 2008[88]

Woods and colleagues conducted a multicentre prospective service review in four specialist dermatology centres in the UK (Hope Hospital, Manchester; St John's Institute of Dermatology, London; Royal Victoria Infirmary, Newcastle upon Tyne; Royal Gwent Hospital, Newport) in 2004 and 2005. Two of the aims of their study of greatest interest to this guideline were to identify variables that might predict length of inpatients stay, including measures of disease severity, and investigate the effectiveness of inpatient stay as measured by the proportion achieving at least a PASI50 or PASI75.

The results of their review confirmed that length of stay increases with disease severity and that inpatient admission was effective, with 30% of patients achieving a PASI75 or above and 65% achieving a PASI50 or above at discharge from hospital. 58% also experienced at least a 50% reduction in their DLQI score and 27.4% had at least a 75% reduction. Woods and colleagues also reported the time taken to achieve a PASI50 in three groups of psoriasis severity, according to PASI at admission. These are presented in Table 58.

Table 58: Time taken to PASI50 based on disease severity

Disease severity at admission	Mean length of stay (days)	Percent of patients achieving PASI50	Mean length of stay (days) to achieve PASI50
PASI <10	15.8	52%	19.2
PASI 10 to 20	20.8	65%	20.7
PASI >20	23.7	83%	24.4

(a) Adapted from Woods and colleagues[88]

P.3.4 Department of Health (DoH) Hospital Episode Statistics (HES) data

Woolacott and colleagues used data from the 2002-03 DoH HES to estimate the length of stay for patients whose psoriasis remains uncontrolled. The data at the time could be expected to reflect care prior to the introduction of biologic therapy into the NHS. Table 59 shows how the mean length of stay for psoriasis appears to have decreased since then (19.6 days in 2002-03 to 12.1 days in 2010-11). As has been reflected in the two cohort studies, this might be explained by reductions in the length of stay for high-need patients upon initiation of biologic therapy.

Although mean length of stay has decreased, the total number of admissions has increased and the proportion of those admissions which are classified as day cases appears to have increased. These changes are thought to reflect changes to the service configuration over the last decade and the way in which infliximab infusions are coded for costing purposes. Historically, patients were admitted for lengthy periods for intensive treatment with dithranol, tar and/or UVB. Now, many of these admissions will have been converted into day centre attendances. Infliximab infusions are often

coded as a day case procedure or a regular day/night admission; however, the relative proportion of the total biologic cohort receiving infliximab is quite small given the stricter NICE eligibility criteria.

Table 59: DoH HES data for diagnosis of psoriasis vulgaris (L40.0)

	2002-03	2004-05	2006-08	2008-10	2010-11
Total admissions	873	667	887	1008	1279
Mean length of stay	19.6 days	18.1 days	16.8 days	15.1 days	12.1 days
Number of day cases	341	135	347	505	860

P.4 GDG experience and opinion

The GDG has indicated that best supportive care is difficult to define because of the heterogeneous population and lack of clear clinical alternatives. The population is likely to have significant co-morbidities, many of which may have been induced by previous treatments for their psoriasis (liver fibrosis, hypertension, renal impairment) and have been the reason for initiating treatment with biologic therapy. The other significant co-morbidity is psoriatic arthritis, which may be found in more than half of psoriasis patients with moderate to severe disease. Biologic therapy has also been shown to be effective in the treatment of psoriatic arthritis. Biologic therapy is also initiated following non-response to methotrexate or following non-response, lost response and/or rapid relapse upon withdrawal of ciclosporin. It also follows on from a patient reaching a maximum cumulative exposure to PUVA, which has put them at increased risk of skin cancer. In summary, a variety of factors make it difficult to consider revisiting previously trialled therapies such as these.

NICE guidance states that treatment with a biologic should be discontinued if an adequate response (PASI75 or PASI50 and 5-point drop in DLQI) is not achieved within 10 to 16 weeks (exact time point depends on the biologic therapy). The clinicians on the GDG indicated that many patients will be maintained if they achieve a PASI50 regardless of a drop in DLQI, but their assumption is that DLQI will have improved and that for most patients a PASI50 is an acceptable improvement given the problems associated with the alternatives (i.e. conventional systemic therapies).

The GDG has also indicated that in current practice, if treatment with a second-line biologic is unavailable, then when a patient loses response (secondary non-responder) after some time, they may not necessarily discontinue treatment given the problems associated with alternative treatments (e.g. conventional systemic therapies). Instead they will follow one of several pathways:

1. Continue treatment, maintaining a suboptimal response (PASI50 or less)
2. Continue treatment, adding in methotrexate or, very rarely, ciclosporin (lower doses than when used as monotherapy) or UVB
3. Continue treatment and increase the dose (if etanercept or adalimumab) or decrease the interval between infusions (if infliximab)

The thought is that options 2 and 3 will not necessarily improve response very much, but may help to maintain at least a PASI50. The reason that clinicians give for continuing patients on marginally effective biologic therapy is that there are few safe and/or effective alternatives. As is clear from the data, some patients will have switched to biologic therapy due to ineffectiveness of other treatments, but many will also have switched due to the toxic adverse events associated with long term use of conventional systemic therapies.

P.5 Best supportive care in the NCGC model

Based on discussions within the GDG, evidence from two retrospective cohort studies and assumptions made in previous NICE technology appraisals, the following definition for best supportive care was used in the NCGC model. It is broken up into different resource categories and then summarised at the end in a single table (Table 50)

P.5.1 Drug and other treatments

As outlined in section P.4, there is recognition that at the point at which patients become eligible for a first biologic therapy, they must have exhausted treatment options such as conventional systemic therapy and phototherapy, including PUVA. Therefore, it may seem paradoxical to include these treatments as possible therapies post-biologic therapy. It was felt that although these therapies had either proved ineffective or given rise to certain toxicities, the patients for whom a second biologic was being considered were unlikely to go without treatment altogether. In the absence of a second biologic therapy, the likelihood is that they would be cycled through different modalities, accepting the associated risks. On this basis, the NCGC model has attempted to approach the treatments comprising 'best supportive care' in a pragmatic fashion, albeit with limitations.

Drugs included under 'best supportive care' and the proportions of patients receiving each were defined by the GDG in the following way:

- 45% of patients will be managed with ciclosporin for a maximum of 2 years
- 45% of patients will be managed with methotrexate
- 10% will be managed with no active pharmacological treatment (some patients will opt for no treatment given the possible risks associated with conventional systemic therapies)

These proportions were varied in sensitivity and scenario analyses.

According to both cohort studies, around 35% of patients have taken fumarates in the year prior to starting biologic therapy. The GDG has indicated that based on this, one could reasonably assume that 65% of patients failing a biologic could trial a course of fumarates. Unfortunately, fumarates are not licensed in the UK and are therefore outside the scope of the guideline.

P.5.2 Health care resource use

P.5.2.1 Outpatient attendances

Both cohort studies showed that there was no significant difference between the number of outpatient attendances during the pre-biologic period and during the first year of biologic therapy. The UK study[89] showed the mean number of outpatient visits to be around 3.2 and the Dutch study[87] showed the mean number to be around 7.2. Woolacott and colleagues[84] based their estimates on expert opinion and assumed that

- patients receiving ciclosporin would have 6-7 visits annually
- patients receiving methotrexate would have 4-5 visits annually
- patients receiving best supportive care (i.e. no active treatment) would have 2 visits annually

In the NCGC model we have assumed there to be no difference between outpatient attendances on best supportive care and biologic treatments and we will assume that there is no difference between ciclosporin and methotrexate under BSC. We have estimated the number of annual outpatient visits to be 4 (i.e. every 3 months). This is slightly higher than the estimate in the cohort study by Fonia and colleagues; however, the group of patients included in the NCGC model are likely to be even

more high-need than those included in the cohort study given that they have already failed at least one biologic therapy.

P.5.2.2 Drug monitoring and laboratory tests

Patients undergoing pharmacological treatment with conventional systemic therapies (i.e. methotrexate or ciclosporin) are assumed to be monitored at regular intervals during treatment. Frequency of monitoring used in the model (Table 60) was informed by estimates used in Woolacott and colleagues[84] and GDG experience. It was assumed that some of these tests will be undertaken as part of outpatient visits and the remainder will be performed outside of an outpatient visit.

Table 60: Resource use: outpatient and laboratory tests

	Ciclosporin	Methotrexate
Outpatient visits		
Annually (maintenance)	4	4
Laboratory tests (annual maintenance)		
FBC	4	4
LFT	4	4
Serum Creatinine	4	4
Urea & Electrolytes	4	4
PIIINP	-	4
Glomerular Filtration Rate	1	-
Liver biopsy	-	0.4 (a)

(a) Frequency of liver biopsy with methotrexate with concurrent use of PIIINP test was based on estimates from Chalmers and colleagues[86]

P.5.2.3 Phototherapy

We have assumed that 16% of patients will undergo one course of narrowband UVB each year (24 sessions). This is based on the estimated use of PUVA in the Driessen study[87] during the year prior to initiation of biologic therapy. Given the high probability of contraindication to PUVA in the hypothetical population of the NCGC model, a course of narrowband UVB was thought to me more realistic than further PUVA.

P.5.2.4 Day-care attendances

Fonia and colleagues[89] estimated day care attendances to be quite low in the pre-biologic period (0.14 per patient per year). Driessen and colleagues[87] estimated it to be higher at 5.1 attendances per year before biologics. The GDG indicated that if the service is available, the population included in the NCGC model (failed biologic therapy) is very likely to utilise such services. On this basis, the NCGC model has assumed that all patients receiving BSC will attend a day centre for specialist applied topicals or other specialist treatment 5 times per year.

P.5.2.5 Inpatient admissions and length of stay

Fonia and colleagues[89] estimated inpatient length of stay to be 6.49 days per year before biologics; Driessen and colleagues[87] estimated it to be 14.9 days per year for 82% of patients and 53.0 days per year for 18% of patients. Combining the subgroups in Driessen and colleagues would give a weighted mean of 21.8 days per year (0.82*14.9+0.18*53=21.8).

The observed length of stay from Fonia and colleagues seems low compared to HES data, length of stay listed in the relevant NHS reference costs (between 9 and 15 days per admission) and GDG

opinion. It is difficult to know how applicable the observations from Driessen and colleagues are because they are from a Dutch health system perspective and there may be important differences in terms of service configuration and delivery of care.

For the NCGC model, we took the breakdown in high-need versus very high-need as observed in the Driessen cohort study (82% vs 18%) to inform a weighted average length of stay. In the base case, we assumed that high-need patients (82%) will require one hospital admission per year, which was assumed to correspond to a mean length of stay of 20.8 days (from Woods and colleagues, see section P.3.3 and Table 58). This is much longer than the 6.5 days observed in Fonia and colleagues, but as this is likely to be a higher-need population than their cohort, the GDG considered this to be a reasonable assumption.

In the base case, we assumed that very high-need patients (18%) will require 2.55 hospital admissions per year, each also 20.8 days in length, which equals out to 53 inpatient days per year, the figure reported for this population in Driessen and colleagues[87].

Given that these variables are quite uncertain extensive sensitivity analyses were performed to explore how small and large changes might affect the cost-effectiveness of second line biologic therapy. In particular, the proportions of high- and very-high need patients and the number of annual admissions and mean length of stay per group were varied.

P.6 Summary of NCGC model assumptions

The working definition of best supportive care, in the context of patients with moderate to very severe plaque psoriasis who are being considered for further biologic therapy, is summarised in terms of resource use in Table 50. This is based on several different sources of information and supplemented by GDG experience and opinion. This defined package of services is expected to cost an annual £10,731. It is worth noting that previous NICE technology appraisals have estimated this cost to be at most £5,328 (based on 21 days in hospital plus 2 outpatient visits per annum). Due to substantial uncertainties in these model parameters, they were subject to extensive sensitivity analyses, each of which was considered by the GDG as they looked to make guideline recommendations that would represent an effective and cost-effective use of NHS resources.

Table 61: Assumed resource use for best supportive care

	Total annual cost			
Component	**Proportion receiving**	**Resource use components**		**Total Cost**
Drugs				
Methotrexate	45% (a)			£228
Ciclosporin (b)	45% (a)			£1,107
No drug	10% (a)	5 OP visits		£41
Other treatment				
Day centre care	100% (a)	5 visits		£1,813
NBUVB	16% (c)	1 course	24 sessions	£327
Inpatient care (g)				
High need	82% (d)	1 admission (a)	20.8 days per admission (f)	£4,625
Very high need	18% (d)	2.55 admissions (e)		£2,589
TOTAL				**£10,730 (h)**

(i) Based on GDG opinion
(j) Maximum treatment 2 years; after 2 years then no drug
(k) Based on proportion receiving PUVA in year before starting biological therapy in Driessen and colleagues[87]

(l) Based on split in Driessen and colleagues(under/over 30 days in hospital per annum)

(m) Calculated based on mean length of stay from Woods[88] (20.8) and mean in hospital days per annum in the very high need group in Driessen[87] (53.0).

(n) Based on mean length of stay for patients admitted with baseline PASI 10 to 20 in Woods[88]. 23.7 days used in sensitivity analysis.

(o) Weighted average length of stay equals 26.6 days per year per patient (20.8[0.82*1+0.18*2.55]=26.6) and weighted average cost equals £7,214 per patient.*

(p) Note: previous TAs[79-82] have estimated this cost to be approximately £5,327.71 (21 days in hospital + 2 outpatient visits per annum)

Appendix Q:Additional data

Q.1 Disease severity and impact assessment tools: summary of non-comparative data

Study	Population	Setting	N	Tool	Data/method of analysis				Conclusion/summary
					Internal consistency (Cronbach's α)	Intra-rater reliability	Inter-rater reliability	Sensitivity to change	
Severity									
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	BSA (PREPI method)	×	✓	✓	✓	• Adequate test-retest reliability (ICC = 0.99/0.98 for number of palms and categorised score) • Inter-rater reliability (self-estimated vs physician estimated): o Visit 1: number of palms (ICC = 0.82) / categorized score (ICC = 0.80) o Visit 2: number of palms (ICC=0.68) / categorized score (ICC = 0.71) • Adequate sensitivity to change: patient measure (AUC = 0.7-0.73); physician measure (AUC = 0.76-0.81) • Practicability: 2-3 mins to administer
Ramsay et al (1991)	Chronic plaque psoriasis	In-patients – Secondary/tertiary care	10	BSA (rule of nines)	×	✓	✓	×	• Acceptable intra-rater reliability (differences of 1-2%; p>0.05 ANOVA)

Study	Population	Setting	N	Tool	Data/method of analysis				Conclusion/summary
					Internal consistency (Cronbach's α)	Intra-rater reliability	Inter-rater reliability	Sensitivity to change	
									• Poor inter-rater reliability (significantly different p<0.001 ANOVA)
Yune et al (2003)	Psoriasis	Secondary/tertiary care (Korea)	30	BSA (visual grading)	×	×	✓	×	• Poor inter-rater reliability (statistically significantly different: p<0.05, Kruskal-Wallis test)
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	CoPSI	×	✓	✓	×	• Adequate test-retest reliability (ICC=0.95) • Adequate inter-rater reliability (ICC=0.83)
Kacar et al (2008)	Nail psoriasis	Secondary/tertiary care	45	NAPSI	×	×	✓	×	• Acceptable inter-rater reliability (r = 0.768)
Aktan et al (2007)	Nail psoriasis	Outpatient clinic – Secondary/tertiary care	25	NAPSI	×	×	✓	×	• Poor inter-rater reliability (ICC = 0.781)
Faria et al (2010)	Psoriasis	Ambulatory clinic	20	PASI	×	×	✓	×	• Adequate to acceptable inter-rater reliability (r = 0.729-0.817)
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary/ care	19	PASI	×	✓	×	×	• Adequate test-retest reliability (r = 0.91)
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PASI	×	✓	✓	×	• Adequate test-retest reliability (ICC=0.96) • Adequate inter-rater reliability (ICC=0.91)
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	20	PASI	×	×	✓	✓	• Acceptable inter-rater reliability (r = 0.71)

Study	Population	Setting	N	Tool	Data/method of analysis				Conclusion/summary
					Internal consistency (Cronbach's α)	Intra-rater reliability	Inter-rater reliability	Sensitivity to change	
									• Adequate responsiveness (significant decrease in extent and psychosocial impact scores; p<0.0001)
Chandran et al (2009)	Psoriatic arthritis	Secondary/tertiary care (Canada)	20	PASI, LS-PGA, PGA, BSA	×	×	✓	×	• Inter-rater variation (rheumatologists vs dermatologists) poor for PASI, LS-PGA, PGA, BSA (0.2-0.8)
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PASI, PGA, LS-PGA	✓	✓	✓	×	• Adequate internal consistency (α≥0.9 for each) • Reliability: PGA and LS-PGA better than PASI • Intra-rater variation by ANOVA: PASI σ = 2.5; PGA σ = 0.2; LS-PGA σ = 0.5 • Inter-rater variation by ANOVA: PASI σ = 8.8; PGA σ = 1.2; LS-PGA σ = 1.7
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	PASI, PGA, LS-PGA	×	✓	✓	×	• Adequate intra-rater reliability for PASI (ICC = 0.94) and LS-PGA (ICC = 0.91); acceptable for PGA (ICC = 0.88) • Adequate inter-rater reliability for PASI (ICC = 0.90) and LS-PGA (ICC =0.84); acceptable for PGA (ICC = 0.75)
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PGA	×	✓	✓	×	• Acceptable test-retest reliability (ICC=0.81)

Study	Population	Setting	N	Tool	Data/method of analysis				Conclusion/summary
					Internal consistency (Cronbach's α)	Intra-rater reliability	Inter-rater reliability	Sensitivity to change	
									• Acceptable inter-rater reliability (ICC=0.61)
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/tertiary care	30	PGA (photographs)	×	✓	✓	×	• Acceptable intra-rater reliability (ICC = 0.84) • Acceptable inter-rater reliability (ICC = 0.80)
Fleischer et al (1996)	Psoriasis	Secondary/tertiary care	30	SAPASI	×	×	✓	×	• Adequate inter-rater reliability (97% agreement)
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary/ care	19	SAPASI	×	✓	✓ (40 body silhouettes)	×	• Adequate test-retest reliability (r = 0.82) • Adequate inter-rater reliability for BSA (ICC = 0.953)
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	20	SPI	×	×	✓	×	• Adequate- adequate - acceptable inter-rater reliability (r = 0.997, 0.86 and 0.70 for the psychological impact, historical disease severity and extent scores)
Impact									
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	DLQI	✓	×	×	×	• Adequate internal consistency (α= 0.89 at baseline, 0.92 at end point)
Shikiar et al (2003)	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	1095	DLQI	✓	×	×	×	• Adequate internal consistency (α= 0.87 at baseline, 0.92 at end point)

Study	Population	Setting	N	Tool	Data/method of analysis				Conclusion/summary
					Internal consistency (Cronbach's α)	Intra-rater reliability	Inter-rater reliability	Sensitivity to change	
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	DLQI	✓	×	×	×	• Adequate internal consistency (α=0.88)
McKenna et al (2005)	Psoriasis	Hospital – Secondary/tertiary	72	DLQI	✓	✓	×	×	• Adequate internal consistency (α≥0.88) • Acceptable test-retest reliability (r=0.80)
Morgan et al (1997)	Psoriasis (attending phototherapy unit)	Out-patients – Secondary/tertiary	41	DQOLS	×	✓	×	×	• Acceptable test-retest reliability (ICC = 0.84)
Nijsten et al (2006)	Psoriasis (first treated with PUVA)	University centres (USA)	792	IPSO	✓	×	×	×	• Adequate internal consistency for physical and psychological scales (0.85 and 0.73); acceptable for social scale (0.63)
Nijsten et al (2005)	Cutaneous psoriasis	Survey of US patients	1196	PDI	✓	×	×	✓	• Adequate internal consistency for subscales (α≥0.77-0.81) • Large floor effects and sub-optimal response distributions
Gupta and Gupta (1995)	Psoriasis in-patients and out-patients	Secondary/tertiary care	217	PLSI	✓	×	×	×	• Adequate internal consistency (α= 0.90)
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	PSORIQoL	✓	✓	×	×	• Acceptable test-retest reliability (ICC = 0.89) • Adequate internal consistency (α=0.94)

Study	Population	Setting	N	Tool	Data/method of analysis				Conclusion/summary
					Internal consistency (Cronbach's α)	Intra-rater reliability	Inter-rater reliability	Sensitivity to change	
McKenna et al (2005)	Psoriasis	Hospital – Secondary/tertiary	72	PSORIQoL (US version)	✓	✓	×	×	• Adequate internal consistency (α≥0.88) • Adequate test-retest reliability (Spearman's r = 0.90)

Q.2 Disease severity and impact assessment tools: summary of comparative data

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
Severity compared with impact								
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	DLQI	PASI, PGA	×	✓	• Acceptable sensitivity to clinically meaningful change (r = 0.69 vs PASI and 0.71 vs PGA) • Significant difference in improvement on DLQI between responders (PASI75) and non-responders (<PASI50)
Shikiar et al (2003)	Moderate-to-severe psoriasis	Secondary/tertiary care (North America)	1095	DLQI	PASI, PGA	✓	✓	• Adequate divergent construct validity vs PASI (r = 0.20 and 0.25 at baseline; 0.51 and 0.59 at end point)

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
		Includes data from 2 separate studies						• Poor sensitivity to change (r = 0.47 and 0.54 compared with PASI; 0.46 and 0.53 compared with PGA) • Significant difference in improvement on DLQI between responders (PASI75 or PASI50) and non-responders (<PASI50)
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	DLQI, Skindex, IPSO, PDI, PLSI	PASI, Skindex symptoms scale	✓	×	• Poor correlation (adequate divergent construct validity) between: PASI and PLSI, PDI, DLQI, IPSO and Skindex; Skindex symptoms scale and PLSI, PDI, DLQI, IPSO.
Kirby et al (2001)	Psoriasis in-patients and out-patients	Hospital (UK)– Secondary/tertiary / care	101	PDI	SAPASI, PASI, SPI	✓	×	• Adequate divergent construct validity (r = 0.50-0.52)
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	PDI	PASI, SAPASI	✓	×	• Adequate divergent construct validity (r = 0.45 and 0.27 vs PASI and SAPASI, respectively)
Finlay et al (1990)	Psoriasis in-patients and out-patients	Secondary/tertiary care	32	PDI	PASI	✓	×	• Adequate divergent construct validity (r = 0.40)
Kotrulja et al (2010)	50% psoriasis	Hospital – Secondary/tertiary care	140	PLSI	PASI	✓	×	• Adequate divergent construct validity (r = 0.30)
Dommasch et al (2010)	Psoriasis	Secondary/tertiary care (USA)	140	Skindex-29	BSA (PREPI method)	✓	×	• Adequate divergent construct validity (r = 0.59)

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
Shanker et al (2011)	Psoriasis	Secondary/tertiary care	34	PQOL-12	PASI	✓	×	• Adequate divergent construct validity (r = 0.422)
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	SPI subscales	PASI, SAPASI, PDI	✓	×	• Adequate divergent construct validity (r = 0.59 and 0.28 psychological impact score vs PDI and PASI, respectively)
Severity								
Henseler and Schmitt-Rau (2008)	Moderate-to-severe chronic plaque psoriasis	Secondary/tertiary care (clinical trial)	33	BSA, PASI, SAPASI	BSA, PASI, SAPASI	✓	✓	• Adequate construct validity for all comparisons (r > 0.7) SAPASI vs PASI: r = 0.91 (p<0.0001) SAPASI vs BSA; r = 0.73 (p<0.0001) PASI vs BSA; r = 0.81 (p<0.0001) • Sensitivity to change: relative change SAPASI>PASI>BSA SAPASI = 70.6%; PASI = 67.3%; BSA = 48.6%
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	CoPSI	PASI, PGA	✓	×	• Adequate construct validity (r = 0.89 vs PASI and r = 0.75 vs PGA)
Shikiar et al (2006)	Moderate-to-severe plaque psoriasis	Clinical trial (multicentre – North America)	147	PASI	PGA	✓	✓	• Adequate construct validity (r = 0.83 at trial end point), but poor construct validity (r = 0.59) at baseline • Acceptable sensitivity to clinically meaningful change (r = 0.75) Note: mean score reduction for PASI was 56.5% and for PGA was 39.1%

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
Kirby et al (2001)	Psoriasis in-patients and out-patients	Hospital (UK)– Secondary/tertiary / care	101	PASI	SAPASI	✓	×	• Acceptable construct validity (r = 0.65)
Berth-Jones et al (2008)	Chronic plaque psoriasis	Unclear	16	PASI	PGA	✓	×	• Adequate construct validity (r = 0.75)
Robinson et al (2011)	Moderate to severe psoriasis	Secondary/tertiary care – receiving biologics	?	PASI	PGA	✓	×	• Adequate construct validity for correlation of PASI75 and PGA 0 or 1
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	PASI	SAPASI	✓	×	• Poor construct validity (r = 0.54)
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	PASI	SAPASI	✓	×	• Acceptable correlation between: SAPASI and PASI
Krenzer et al (2011)	Moderate to severe plaque psoriasis receiving efalizumab	Out-patient departments and dermatological practices	1787	PASI	BSA	✓	✓	• Poor to adequate construct validity (r = 0.450 at baseline; 0.694 at 3 months and 0.832 at 6 months) • Acceptable sensitivity to change (r= 0.771 after 3 months and 0.792 after 6 months)
Langley et al (2004)	Psoriasis out-patients	Secondary/tertiary care (USA)	35	PASI, PGA, LS-PGA	PASI, PGA, LS-PGA	✓	×	• Adequate construct validity for all comparisons (r > 0.8)
Berth-Jones et al (2006)	Chronic plaque psoriasis	Secondary/tertiary care (UK)	16	PASI, PGA, LS-PGA	PASI, PGA, LS-PGA	✓	×	• Adequate construct validity for all comparisons (r > 0.7): LS-PGA vs PASI: r = 0.92 LS-PGA vs PGA; r = 0.73 PGA vs PASI; r = 0.79

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
Farhi et al (2008)	Plaque psoriasis	Out-patient and phototherapy unit – Secondary/tertiary care	30	PGA (photographs)	Clinical PGA	✓	×	• Acceptable construct validity (ICC = 0.64) • Adequate construct validity for mean panel score (ICC = 0.87)
Iyatomi et al (2009)	Mild psoriasis vulgaris	Secondary/tertiary care	5	Photographs (computer quantification)	PASI	✓	×	• Adequate construct validity (r = 0.922) • Sensitivity = 72.1%; specificity = 97.4% (vs clinical assessment)
Sampogna et al (2003)	Psoriasis in-patients	Hospital (Italy)– Secondary/tertiary care	351	SAPASI	PASI	✓	×	• Acceptable construct validity (r = 0.69)
Fleischer et al (1999)	Psoriasis	Clinical trial – Secondary/tertiary care	182	SAPASI	PASI-equivalent	✓	✓	• Poor construct validity (r = 0.54 at baseline; r = 0.33 at endpoint) • SAPASI less sensitive to change (r=0.16): Decrease in severity 39% vs 62% for SAPASI and PASI respectively
Feldman et al (1996)	Psoriasis	Hospital (USA)– Secondary/tertiary / care	80	SAPASI	PASI	✓	×	• Poor construct validity on first day: r = 0.58 • Adequate construct validity on second day: r = 0.70 • BSA determinations: Head: r = 0.62 (acceptable) Upper extremities r = 0.75 (adequate) Trunk: r = 0.73 (adequate) Lower extremities: r = 0.69 (acceptable) • Erythema, induration and scale scores: Erythema: r = 0.39 (poor)

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
								Induration: r = 0.24 (poor) Scale: r = 0.38 (poor)
Feldman et al (1996)	Psoriasis	Hospital (USA)–Secondary/tertiary / care	30	SAPASI	PASI	×	✓	• Acceptable sensitivity to change (change in SAPASI vs change in PASI score (r = 0.63)
Szepietowski et al (2001)	Psoriatic (40 psoriasis vulgaris, 11 PsA)	Unclear	51	SAPASI	PASI	✓	×	• Acceptable construct validity (r = 0.62)
Szepietowski et al (2001)	Psoriatic (40 psoriasis vulgaris, 11 PsA)	Unclear	51	SAPASI	SPI extent score	✓	×	• Acceptable construct validity (r = 0.62)
Fleischer et al (1994)	Psoriasis vulgaris	Secondary/tertiary care (USA)	42	SAPASI	PASI	×	✓	• Mean decrease in score: PASI = 7.3±5.7; SAPASI = 5.9±4.7 • Both showed significant improvements: PASI p<0.0003; SAPASI p<0.05
Impact								
Nichol et al (1996)	Psoriasis (upto 20% BSA)	Clinical trial (US multicentre)	644	DLQI	PDI	✓	×	• Adequate construct validity (r = 0.82)
McKenna et al (2003)	Psoriasis	Postal survey from hospital database	148	PSORIQoL	DLQI	✓	×	• Adequate construct validity (r = 0.70)
McKenna et al (2005)	Psoriasis	Hospital	72	PSORIQoL (US version)	DLQI	✓	×	• Adequate construct validity (r = 0.81)

Study	Population	Setting	N	Tool	Comparison	Data/method of analysis		Conclusion/summary
						Construct validity (correlation coefficient)	Sensitivity to change	
Sampogna et al (2004)	Psoriasis in-patients	Secondary/tertiary care (Italy)	786	Skindex, IPSO, DLQI, PDI, PLSI	Skindex, IPSO, DLQI, PDI, PLSI	✓	×	• Acceptable correlation between: Skindex social function scale and PLSI; Skindex emotions scale and PLSI, PDI, DLQI; DLQI and PLSI; PDI and PLSI • Adequate correlation between: IPSO and PLSI, PDI and DLQI; DLQI and PDI; Skindex social functioning scale and PDI, DLQI, IPSO; Skindex emotions scale and IPSO
Kirby et al (2000)	Psoriasis	Secondary/tertiary care	100	SPI subscales	PDI	✓	×	• Poor construct validity (r = 0.59 for psychological impact score vs PDI)

Q.3 Quality assessment for disease severity and impact tool validity and reliability studies

Q.3.1 Internal consistency reliability – single measurement, multiple people

Study	Same measurement procedure	Same measuring instrument	Same environmental conditions: (e.g. lighting) and same location	Appropriate statistical analysis	Applicability – analysis method (dichotomised/categorised appropriately/continuous? Who is testing/setting/experience)	Quality
Gupta and Gupta (1995)	✓ - patient self-rating	✓	?	✓	✓	High
Langley et al (2004)	✓	✓	✓	✓	Range of severities No medications used during the study Raters given 30 minute training sessions	High

Study	Same measurement procedure	Same measuring instrument	Same environmental conditions: (e.g. lighting) and same location	Appropriate statistical analysis	Applicability – analysis method (dichotomised/categorised appropriately/continuous? Who is testing/setting/experience)	Quality
McKenna et al (2003)	✓ - patient self-rating	✓	×	✓	✓	High
McKenna et al (2005)	✓ - patient self-rating	✓	×	✓	✓	High
Nijsten et al (2005)	✓ - patient self-rating	✓	×	✓	Psoriasis survey (any severity but n PsA) Categorical rating scale Excluded patients with missing items	High
Nijsten et al (2006)	✓ - patient self-rating	✓	×	✓	PUVA cohort Ordinal rating scale Excluded patients with missing items	High
Shikiar et al (2003)	✓	✓	×	✓	Trial of efalizumab vs placebo	High
Shikiar et al (2006)	✓	✓	×	✓	Trial of adalimumab vs placebo	High

Q.3.2 Intra-rater reliability

Study	Same measurement procedure	Same observer and same measuring instrument	Same environmental conditions: (e.g. Lighting) and the same location	Time between measurements not too long (<1 week)	Appropriate statistics – not correlation	Applicability – analysis method Rater/setting/experience)	Quality
Berth-Jones et al (2006)	✓	✓	✓	✓	✓	✓	High
Berth-Jones et al (2008)	✓	✓	✓	✓	✓	✓	High

Study	Same measurement procedure	Same observer and same measuring instrument	Same environmental conditions: (e.g. Lighting) and the same location	Time between measurements not too long (<1 week)	Appropriate statistics – not correlation	Applicability – analysis method Rater/setting/experience)	Quality
Dommasch et al (2010)	✓	✓	× - home and clinic	✓	✓	✓ Self-administered (categorised and continuous assessed)	Moderate
Farhi et al (2008)	✓	✓	?	NA - 1 month but same set of photographs	✓	✓	Moderate
Feldman et al (1996)	✓	✓	?	✓	×	✓	Low
Kirby et al (2000)	✓	✓	✓	✓	×	?	Moderate
Langley et al (2004)	✓	✓	✓	✓	× ANOVA	Range of severities No medications used during the study Raters given 30 minute training sessions Spearman's coefficient	Moderate
McKenna et al (2003)	✓	✓	? completed by postal survey	× 2 weeks	×	✓	Very low
McKenna et al (2005)	✓	✓	? completed by postal survey	× 2 weeks	✓	✓	Very low
Morgan et al. (1997)	✓	✓	?	× 7-10 days	✓	Out-patients attending for phototherapy	Very low
Ramsay et al (1991)	✓	✓	? – likely because in-patients	✓ - recall bias minimised by randomising order of	× - simple agreement	In-patients Assessed by 3 dermatologists and 1 dermatology specialist nurse Continuous	Low

Study	Same measurement procedure	Same observer and same measuring instrument	Same environmental conditions: (e.g. Lighting) and the same location	Time between measurements not too long (<1 week)	Appropriate statistics – not correlation	Applicability – analysis method Rater/setting/experience)	Quality
				assessment of body areas			

Q.3.3 Inter-rater reliability

Study	Number of raters	Randomisation of raters to patients (including order of raters)	Blinding of raters results to results of other raters	Time between measurements not too long (<1 week)	Appropriate statistics – not correlation	Applicability – analysis method Rater/setting/experience)	Quality
Aktan et al (2007)	3	?	✓	✓ - also same conditions and well illuminated	✓	Dermatology out-pt clinic Dermatologists – reviewed NAPSI paper Continuous	Moderate
Berth-Jones et al (2006)	14	✓	✓	✓	✓	14 physicians chosen to represent a range of experience – all received detailed training Ordinal scores treated as continuous variables	High
Berth-Jones et al (2008)	14	✓	✓	✓	✓	14 physicians chosen to represent a range of experience – all received detailed training	High

Study	Number of raters	Randomisation of raters to patients (including order of raters)	Blinding of raters results to results of other raters	Time between measurements not too long (<1 week)	Appropriate statistics – not correlation	Applicability – analysis method Rater/setting/experience)	Quality
						Ordinal scores treated as continuous variables	
Farhi et al (2008)	5	×	✓	✓	✓	Experienced raters Unclear if continuous	Moderate
Faria et al (2010)	3	×	✓	✓	✓ but only pairwise ICC (not for all 3 raters combined)	Post-graduate dermatology students Psoriasis ambulatory clinic	Moderate
Feldman et al (1996)	5	NA	✓	NA	✓	Dermatologists and psychologists	High
Fleischer et al (1996)	2	NA	?	NA	× - simple agreement	A priori categorisation	Low
Kacar et al (2008)	2	× - same order	?	✓ - same day and same conditions	× - Pearson's correlation coefficient	?	Very low
Kirby et al (2000)	6	?	?	✓	×	6 trained raters	Low
Langley et al (2004)	17	✓	✓	✓	× ANOVA	Range of severities No medications used during the study Raters given 30 minute training sessions	Moderate

Q.3.4 Construct validity/sensitivity to change

Study	Time between measurements not too long (<1 week)	Test order randomised	Both tests conducted in each patient	Tests conducted by the same raters (or raters randomised to tests and blinded to other raters results)	Applicability – analysis method and rater/setting/experience)	Quality
Berth-Jones et al (2006)	✓	✓	✓	✓	✓ - categorising defined a priori 14 dermatologists with a range of experience (all trained) Ordinal scores treated as continuous variables	High
Berth-Jones et al (2008)	✓	✓	✓	✓	✓ - categorising defined a priori 14 dermatologists with range of experience (all trained) Ordinal scores treated as continuous variables	High
Dommasch et al (2010)	✓	NA for physician vs self-administered tests	✓	✓ - patient and physician blinded	Dermatology department	High
Farhi et al (2008)	✓	×	✓	× photos by 5 raters and clinical PGA by one	Photo – 5 senior dermatologists with experience	Low
Feldman et al (1996)	✓	NA for physician vs self-administered tests	✓	✓ Physician blind to patient rating	Experienced raters Continuous	High
Finlay et al (1990)	✓	NA for physician vs self-administered tests	✓	× - patient and physician not blinded	Dermatology in and out-patients Continuous	Low
Fleischer et al (1994)	✓	NA for physician vs self-administered tests	✓	✓ Physician blind to patient rating	Dermatology in and out-patients Continuous	High

Study	Time between measurements not too long (<1 week)	Test order randomised	Both tests conducted in each patient	Tests conducted by the same raters (or raters randomised to tests and blinded to other raters results)	Applicability – analysis method and rater/setting/experience)	Quality
Fleischer et al (1999)	✓	NA for physician vs self-administered tests	✓	✓ Physician blind to patient rating	Dermatology in and out-patients Continuous	High
Henseler and Schmitt-Rau (2008)	✓	NA for physician vs self-administered tests	✓	× - patient and physician not blinded	Treated group – efalizumab Outpatient Transformation of continuous scales to map onto each other stated	Low
Iyatomi et al (2009)	?	×	✓	×	3 treated with CSA and 2 with UVB	Very low
Kirby et al (2000)	✓	? NA for physician vs self-administered test comparisons	✓ - SAPASI in only 72%	✓	Spearman's correlation coefficient Method unclear Experienced clinicians	High (PASI vs SAPASI; SPI vs SAPASI; PDI vs PASI) Moderate (PASI vs SPI; PDI vs SAPASI)
Kirby et al (2001)	? probably same day	? NA for physician vs self-administered test comparisons	✓	× One of 3 raters – not randomised	Spearman's coefficient Method unclear Experienced clinicians	High (PASI vs SAPASI; SPI vs SAPASI; PDI vs PASI) Moderate (PASI vs SPI; PDI vs SAPASI) Moderate (PASI vs SPI; PDI vs SAPASI)

Study	Time between measurements not too long (<1 week)	Test order randomised	Both tests conducted in each patient	Tests conducted by the same raters (or raters randomised to tests and blinded to other raters results)	Applicability – analysis method and rater/setting/experience)	Quality
Kotrulja et al (2010)	✓	NA for physician vs self-administered tests	✓	? unclear if patients and investigators blinded to results of other test	PASI and PLSI categorised a priori	Moderate
Krenzer et al (2011)	✓	×	✓	?	Continuous Pearson's correlations Experience unclear	Moderate
Langley et al (2004)	✓	×	✓	✓	Range of severities No medications used during the study Raters given 30 minute training sessions Spearman's coefficient	Moderate
McKenna et al (2003)	? completed at home so could vary	×	?	✓	Method unclear Self-administered	Low
Nichol et al (1996)	✓	?	✓	✓	Pearson coefficients Scales expressed as a percentage of maximum disability	Moderate
Robinson et al (2012)	✓	?	✓	?	Pearson coefficients Dichotomised outcomes	Moderate
Sampogna et al (2003)	✓	NA for physician vs self-administered tests	✓	? unclear if patients and investigators blinded to results of other test (one self-administered and one physician administered)	Baseline data from in-patient wards of dermatology hospital Pearson coefficient Continuous	Moderate
Sampogna et al (2004)	✓	NA for physician vs self-administered tests	✓	? unclear if patients and investigators blinded to results of	Baseline data from in-patient wards of dermatology hospital Pearson coefficient	Moderate

Study	Time between measurements not too long (<1 week)	Test order randomised	Both tests conducted in each patient	Tests conducted by the same raters (or raters randomised to tests and blinded to other raters results)	Applicability – analysis method and rater/setting/experience)	Quality
				other test (one self-administered and one physician administered)	Continuous	
Shankar et al (2011)	✓	NA for physician vs self-administered tests	✓	?	Continuous	Moderate
Shikiar et al (2003)	✓	NA for physician vs self-administered tests	✓	✓	Continuous and dichotomised (pre-specified) Data from trial of efalizumab vs placebo	High
Shikiar et al (2006)	✓	NA for physician vs self-administered tests	✓	✓	Continuous and dichotomised (pre-specified) Data from trial of adalimumab vs placebo	High
Szepietowski et al (2001)	?	NA for physician vs self-administered tests	✓	? unclear if patients blinded to initial PASI score	Spearman rank correlation	Low

Q.4 Interpreting post-test probabilities by considering prevalence/pre-test probability

Predictive values or post-test probabilities address the chances of a person having a particular diagnosis given the known test result. However, the values are only accurate for a population with similar prevalence to the population tested because the prevalence of disease in the population can have a large effect on the calculated predictive value. Therefore, the predictive values are not independent of prevalence and are not intrinsic to the test itself.

Consequently, it is necessary to consider the prevalence when interpreting the positive and negative predictive values. In this report, the modified positive and negative predictive values have been calculated, which represent the value-added predictive figures:

Value-added PPV = PPV – prevalence

Value-added NPV = NPV – (1 – prevalence)

These figures convey the additional certainty of the diagnosis that is contributed by a positive or negative test result over the starting probability of a diagnosis (the prevalence in the sample). However, it is important to bear in mind that if there is only a small amount of uncertainty in the diagnosis before the test a small absolute increase in certainty may be important for diagnostic decisions.

Below is a summary matrix to aid interpretation of these values when the post-test probability is high, which superficially suggests a high diagnostic accuracy. Note that if the PPV or NPV is low then the test is unlikely to be useful as it will be unable to accurately discriminate a positive from a negative diagnosis in the majority of cases.

Table 62: Interpreting high post-test probabilities

Prevalence (pre-test probability)	Post-test probability (predictive values)	
	PPV high	NPV high
High	Little value added: limited additional certainty in the diagnosis and so uncertain in the discriminative ability of the test (accurately detected those with disease but there was a large proportion of positives in the sample)	Large value added: considerable additional certainty in the negative diagnosis and so high value of the test (accurately detected those without disease from a small total number of negatives)
Low	Large value added: considerable additional certainty in the positive diagnosis and so high value of the test (accurately detected those with disease from a small total number of positives)	Little value added: limited additional certainty in the diagnosis and so limited value of the test (accurately detected those with disease but there was a large proportion of negatives in the sample)

Q.5 Skin cancer – PUVA dose classification

Stern 1984A

Time to tumour (months)	Time to follow-up interview (months)	PUVA exposure (number of treatments)*		
		Low	Medium	High
22-27	24	<80	80-99	>99
28-39	35	<100	100-119	>119
40-57	47	<100	100-139	>139
58-69	60	<120	120-159	>159
>69	70	<120	120-159	>159

**Average dose of UVA to body is 11 joules/cm^2 per treatment*

Stern 1994

Time to tumour (months)	Time to follow-up interview (years)	PUVA exposure (number of treatments)*		
		Low	Medium	High
0-27	2	<80	80-99	>99
28-39	3	<100	100-119	>119
40-57	4	<100	100-139	>139
58-69	5	<120	120-159	>159
70-96	6	<120	120-159	>159
94-136	10	<140	140-239	>239
>136	13	<160	160-299	>299

**Average dose of UVA to body is 11 joules/cm^2 per treatment*

Stern 1990 and 2002

Time to tumour (months)	Time to follow-up interview (months)	PUVA exposure (number of treatments)*		
		Low	Medium	High
0-27	24	<80	80-99	>99
28-39	35	<100	100-119	>119
40-57	47	<100	100-139	>139
58-69	60	<120	120-159	>159
70-96	70	<120	120-159	>159
>96	121	<140	140-239	>239

*Average dose of UVA to body is 11 joules/cm^2 per treatment

Q.6 Skin cancer – absolute risk estimates

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate	Absolute risk estimate
PUVA					
STERN 1979	1380	2.1 years (1976-1979)	BCC SCC	IRR: 2.63 (1.91-3.90)	30 patients had one or more cutaneous carcinomas (11.4 expected) Total observed: 29 SCC in 18 patients; 19 BCC in 15 patients **NOTE: 39 patients had a history of cutaneous carcinoma before PUVA (17% SCC and 83% BCC)**
STERN 1984A	1380	5.7 years	BCC SCC	**Population rates** BCC 2.2 (1.6-2.9) SCC 16.2 (13.0-19.9) **Person counts** BCC 1.7 (1.2-2.3) SCC 9.3 (6.9-12.2)	Numbers observed (at least 22 months after exposure and only counting one tumour of a given type each year): 89 SCC and 43 BCC (51 patients compared with 5.1 expected) Total observed: 169 SCC in 54 patients; 74 BCC in 50 patients
STERN 1988A	1380	Mean >10 years	SCC	**PUVA dose** / **All pts with *first* tumour ≥58 months after first treatment** **RR** / **95% CI** <160: 4.2 (2.6-6.4) 160-199: 22.2 (10.6-40.9) 200-259: 32.1 (18.7-51.4) 260+: 50.1 (24.9-89.5) **Total: *9.5* (*7.2-12.3*)**	**Treatments** / **All pts with *first* tumour ≥58 months after first treatment (number of tumours)** <160: 21 (49) 160-199: 10 (29) 200-259: 17 (52) 260+: 11 (28) **Total: 59 (158)** ⇒ **3.8% increased 10 year risk of SCC** ⇒ **1 excess SCC per 261 people per year**
			BCC	**PUVA dose** / **All pts with first tumour ≥58 months after first treatment (number of tumours)** **RR** / **95% CI** <160: 1.3 (0.8-1.9)	**Treatments** / **All pts with first tumour ≥58 months after first treatment (number of tumours)** <160: 26 (45) 160-199: 7 (11) 200-259: 13 (22)

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate	Absolute risk estimate
				160-199 3.0 1.2-6.3 200-259 4.8 3.5-6.5 260+ 6.9 3.2-13.1 **Total *2.1* *1.6-2.7***	260+ 9 (19) **Total 55 (97)**
STERN 1990	1380	12.3 years	Genital SCC	**SMR (95% CI)** **Invasive SCC of penis and scrotum** *95.7 (43.8-181.8)* **Invasive and in situ penile tumours** *58.8 (26.9-111.7)* **Invasive SCC of scrotum** *131.6* (42.7-307.1)	Numbers observed: 30 genital tumours in 14 patients *21 in 10 patients* *19 in 8 patients* 9 in 5 patients
STERN 2002	1380	>20 years	Invasive genital SCC	**Population counts** *SMR: 134.6 (89.5-194.6)* **Person counts** *SMR: 81.7 (52.1-122.6)*	Numbers observed: 28 incident events 17 person counts
STERN 1994	1380	13.2 years	BCC	**PUVA dose** **N** **SMR (95% CI)** **Population counts (one or more tumour/year = an incident event)** Low 114 3.6 (3.0-4.3) Medium 28 2.9 (2.0-4.2) High 75 6.0 (4.8-7.5) *Total 217 4.1 (3.5-4.7)* **Person counts (only the first tumour of a given type is counted)** Low 66 2.1 (1.6-2.7) Medium 19 1.9 (1.2-3.0) High 45 3.8 (2.8-5.1)	Numbers observed: 341 BCCs in 130 patients Population counts: 217 incidence cases of BCC

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate			Absolute risk estimate
				Total	*130*	*2.5 (2.1-3.0)*	
			SCC	**PUVA dose**	**N**	**SMR (95% CI)**	Numbers observed: 618 SCCs in 144 patients; Population counts: 326 incident cases of SCC ⇨ 12 expected (314 excess in 1380 people over 13.2 years) ⇨ 1723.8 excess per 100000 person years (1 excess per 58 people per year)
				Population counts (occurrence of one or more tumours of a given type in a given year = an incident event)			
				Low	80	10.6 (8.5-13.2)	
				Medium	51	23.6 (18.0-31.1)	
				High	195	83.0 (72.1-95.5)	
				Total	*326*	*27.0* (*24.2-30.1*)	
				Person counts (only the first tumour of a given type is counted)			
				Low	38	5.0 (3.6-6.9)	
				Medium	29	13.4 (9.3-19.3)	
				High	77	32.8 (26.2-41.0)	
				Total	*144*	*11.9* (*10.1-14.0*)	

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate	Absolute risk estimate
STERN 1998A			SCC BCC	**Total PUVA treatments to 1986** — SCC: **RR** / **95% CI** <100: 5.1 (3.5-7.2) 100-159: 8.4 (5.6-12.1) 160-336: 26.5 (22.2-31.4) ≥337: 68.5 (54.9-84.5) *All dosages: 17.6 (15.6-19.8)* **Total PUVA treatments to 1986** — BCC: **RR** / **95% CI** <100: 1.7 (1.2-2.3) 100-159: 3.9 (3.0-5.0) 160-336: 4.5 (3.5-5.7) ≥337: 11.7 (9.3-14.5) *All dosages: 4.1 (3.7-4.6)*	**Exposure** — **Number of patients with cancers developing after 1985 (% in each dose strata)**: **Total** / **SCC** / **BCC** **PUVA treatments up to 1986** <100: 435 (37%) / 18 (13%) / 29 (19%) 100-159: 243 (21%) / 15 (11%) / 30 (20%) 160-336: 373 (32%) / 68 (50%) / 58 (38%) ≥337: 132 (11%) / 34 (25%) / 34 (23%) Total: 1183 / 135 / 151 **Increase in 10-year risk of SCC** <100: **1.7%** 100-159: **2.7%** 160-336: **8.8 %** ≥337: **12.7%**
NIJSTEN 2003A	1380	>20 years	SCC and BCC	At 25 years post-PUVA vs age matched Arizona population: SCC = 25-times the risk (250-times risk if more than 400 treatments) BCC = 50-times risk if more than 500 treatments	**SCC** 2147 invasive SCC in 303 patients Incidence of SCC (age-adjusted) has increased over the 25 years of the study: **Average incidence rate = 77 per 1000 person years** **Incidence rate at 25 years follow-up = approximately 200 per 1000 person years** **BCC** 1363 BCC in 294 persons

<table>
<tr><th>Study</th><th>N with psoriasis</th><th>Follow-up time</th><th>Outcome</th><th>Relative risk estimate</th><th>Absolute risk estimate</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Average incidence has increased substantially over the last 10 y of the study :
Average incidence rate = 44 per 1000 person years
Incidence rate at 25 years follow-up = approximately 125 per 1000 person years

Among patients with 200 or more PUVA exposures approximately half will develop at least one SCC and approximately one third at least one BCC within 25 years of reaching this dose level</td></tr>
<tr><td>LIM2005</td><td>1380</td><td>28 years</td><td>SCC</td><td>IRR (95% CI)

No. UVB treatments
<300[e] 1
≥300 1.37 1.03–1.83
No. treatments
<100[e] 1
100–199 2.36 1.51–3.68
200–299 4.14 2.64–6.50
300–399 5.54 3.38–9.09
400–499 11.05 6.88–17.76
≥500 10.81 6.76–17.29</td><td><table>
<tr><th></th><th>Person years (%)</th><th>Number of tumours (%)</th><th>Tumour incidence per 100,000 person years</th><th>Number of incident tumours (%)</th><th>Incident tumour incidence per 100,000 person years</th></tr>
<tr><td>UVB</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Low (<300)</td><td>20,921 (74.9)</td><td>1538 (60.8)</td><td>7351</td><td>696 (63.0)</td><td>3327</td></tr>
<tr><td>High (≥300)</td><td>7007 (25.1)</td><td>990 (39.2)</td><td>14,129</td><td>408 (37.0)</td><td>5823</td></tr>
<tr><td>PUVA</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Low (<100)</td><td>11,922 (42.7)</td><td>197 (7.8)</td><td>1652</td><td>118 (10.7)</td><td>990</td></tr>
<tr><td>Not low (≥100)</td><td>16,006 (57.3)</td><td>2331 (92.2)</td><td>14,563</td><td>986 (89.3)</td><td>6160</td></tr>
</table></td></tr>
</table>

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate	Absolute risk estimate
			BCC	**IRR (95% CI)** No. UVB treatments <300[e] 1 ≥300 1.45 1.07–1.96 No. treatments <100[e] 1 100–199 1.80 1.21–2.70 200–299 2.00 1.32–3.03 300–399 2.81 1.75–4.51 400–499 2.93 1.73–4.98 ≥500 3.65 2.21–6.03	**Variable** / **Person years (%)** / **Number of tumours (%)** / **Tumour incidence per 100,000 person years** / **Number of incident tumours (%)** / **Incident tumour incidence per 100,000 person years** UVB Low (<300): 20,921 (74.9) / 880 (56.2) / 4206 / 511 (61.8) / 2443 High (≥300): 7007 (25.1) / 686 (43.8) / 9790 / 316 (38.2) / 4510 PUVA Low (<100): 11,922 (42.7) / 256 (16.3) / 2147 / 148 (17.9) / 1241 Not low (≥100): 16,006 (57.3) / 1310 (83.7) / 8184 / 679 (82.1) / 4242
STERN 2001	1380	Mean 22.4 years	Melanoma		**Study period** **All melanoma** **Observed** **Incidence (per 1000 pers. years)** 1975 to 1990 4 0.22 1991 to 29/2/96 10 2.47 29/2/96 to end 11 6.00 All years 25 1.04
Stern 1997	1380	20 years	Invasive melanoma	**RR (95% CI)** <250 treatments 1.3 (0.4-3.1) ≥250 treatments 5.5 (2.0-12.0) **All patients** **2.3 (1.1-4.1)**	**Number of invasive melanomas** **Observed** **Expected** <250 treatments 5 3.7 ≥250 treatments 6 1.1 **All patients** **11** **4.8**

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate	Absolute risk estimate
PUVA + retinoids					
NIJSTEN2003	135	>1 years for retinoids	SCC BCC	IRR for retinoid use SCC: 0.79 (0.65-0.95) BCC: 0.94 (0.67-1.32)	**SCC** Retinoid use: 196 SCC per 1000 person years No retinoid use: 302 SCC per 1000 person years Incidence reduction during years of use = 106 SCCs/1000 person-years (95%CI 173, 22) **BCC** Retinoid use: 118 BCC per 1000 person years No retinoid use: 146 BCC per 1000 person years Incidence reduction during years of use = 28 BCCs/1000 person-years (95%CI 79, -22)
PUVA + CSA					
MARCIL 2001	844	6 months for CSA	SCC	**Treatment** **Multivariate IRR** **Time** 5 years before CSA 1.0 After first CSA 2.1 (2.0-2.5) **CSA use** No 1.0 Yes 3.1 (2.6-3.7) **PUVA treatments to 1992** <200 1.0 ≥200 2.8 (2.6-3.2) **MTX use** <36 months 1.0 ≥36 months 1.7 (1.5-1.9)	**Treatment** **Pts** **SCC** **Patient years** **Time** 5 yr before CSA 844 417 4220 **= 99 per 1000 person years** After first CSA 844 1178 4853 **= 243 per 1000 person years** **CSA use** No 816 1426 8901 **= 160 per 1000 person years** Yes 28 169 172 **= 983 per 1000 person years** **PUVA treatments to 1992** <200 525 514 5571 **= 92 per 1000 person years** ≥200 319 1081 3502 **= 309 per 1000 person years** **MTX use** <36 months 710 1107 7653 **= 145 per 1000 person years** ≥36 months 134 488 1419 **= 344 per 1000 person years**
CSA					

Study	N with psoriasis	Follow-up time	Outcome	Relative risk estimate				Absolute risk estimate					
PAUL 2003	1252	5 years	Skin cancers		Person-years	SIR	95% CI	Cancer	Patients N	(%)	Person-Years	Incidence rate	95% CI
				Any skin malignancy	4330	6.1	3.8–9.1	All skin malignancies	23	1.8	4377	5.3	3.3–7.9
				BCC	4379	1.8	0.6–4.1	BCC	5	0.4	4426	1.1	0.4–2.6
				SCC	4354	24.6	13.8–40.7	SCC	15	1.2	4401	3.4	1.9–5.6
				Malignant melanoma	4384	4.7	0.6–17.0	Melanoma	2	0.2	4431	0.5	0.1–1.6
NBUVB													
HEARN 2008	3867 (2130 [55%] with psoriasis)	Median: 5.5 (3.0-9.0) years	BCC SCC MM	**Cancer**	**Treatments**	**SIR (95% CI)**		Observed in total population (55% psoriasis): 27 first BCC; 7 first SCC; 6 first MM 15 BCC vs 7.9 expected among those with psoriasis treated with both NBUVB and PUVA					
				BCC	TL-01 only	156 (57-339)							
					TL-01 + PUVA	190 (106-313)							
				SCC	TL-01 only	0 (0-465)							
					TL-01 + PUVA	126 (15-454)							
				MM	TL-01 only	105 (3-586)							
					TL-01 + PUVA	157 (32-460)							

Q.7 Comorbidities – absolute risk estimates

Q.7.1 Cardiovascular disease

Study	Outcome	Relative risk estimate	Absolute risk estimate
Ahlehoff 2011E	AF	**IRR** **Mild psoriasis** 1.22 (1.14-1.30) **Severe psoriasis** 1.53 (1.23-1.91)	**Event rates per 1000 observational years** Control: Overall 3.03; <50 0.26; ≥50 6.10 Mild: Overall 4.67; <50 0.36; ≥50 7.21 Severe: Overall 5.96; <50 0.59; ≥50 9.10 Absolute risk difference - mild: Overall 1.64; <50 0.1; ≥50 1.11 Absolute risk difference - severe: Overall 2.93; <50 0.33; ≥50 3 **Excess events overall = 1 in 610 patients per year for mild/ 1 in 341 patients per year for severe** **Attributable risk %** Mild: 18.0% Severe: 34.6%
Ahlehoff 2011B	Composite	**HR (95% CI)** 1.26 (1.06-1.54)	**Incidence rate per 1000 person years (95% CI)** Psoriasis: 185.6 (155.8-221.0) Control: 149.7 (147.1-152.4) **ARD/1000 person years** 35.9
Abuabara	CVD mortality	Cox model HR (95% CI) 1.57 (1.26-1.96)	**Absolute risk/1000 person years** 61.9 **Attributable risk/1000 person years** 3.5 **Excess risk** 1 death per 286 pts/year
Mehta 2010	CVD death	HR 1.57 (1.26, 1.96)	**Incidence per 1000 person-years (95% CI)** Control: 6.19 (5.51, 6.92) Psoriasis: 8.75 (7.18, 10.56) **Based on HR model** Excess risk of CV death attributable to psoriasis of 1 in 283 patients per year (=3.5 excess deaths per 1000 person years)
Mallbris 2004	CVD mortality - inpatients	**Variables** **SMR** **95% CI** Total 1.52 1.44-1.60 Age at first hospitalisation	Incidence during follow-up (0-15+ years; mean not given) **Observed deaths** **Expected deaths** **Difference** Total 1529 1007 522

Study	Outcome	Relative risk estimate			Absolute risk estimate			
		0-19	0.00	0.00-3.74	**Age at first hospitalisation**			
		20-39	2.62	1.91-3.49	0-19	0	0.99	-0.99
		40-59	1.91	1.74-2.09	20-39	46	18	28
		60+	1.37	1.29-1.46	40-59	453	237	216
					60+	1030	750	280
					Note: for those with at least 15 years follow-up observed = 355, expected = 207; so 148 excess deaths over 15+ years (9.9/yr) in 3469 patients followed up for 15+ yr (42.7/1000 patients)			
Mallbris 2004	CVD mortality - outpatients	**Variables**	**SMR**	**95% CI**	Incidence during follow-up (0-15+ years; mean not given)			
		Total	0.94	0.89-0.99	**Variables**	**Obs**	**Exp**	**Difference**
		Age at start of follow-up			Total	1302	1390	-88
		0-19	0.00	0.00-20.3	Age at start of follow-up			
		20-39	0.65	0.26-1.34	0-19	0	0.18	-0.18
		40-59	1.00	0.85-1.16	20-39	7	11	-4
		60+	0.93	0.88-0.99	40-59	161	161	0
					60+	1134	1218	-84
					Note: for those with 10-15 years follow-up observed = 141, expected = 150; so 9 fewer deaths over 10-15 years in 17,328 patients			
Wakkee	IHD	HR 1.05 (0.95, 1.17)			**Outcome**	**Incidence rate**/100,000 person years	**Excess risk**/100,000 person years	
					Ref cohort	559 (522-598)	-	
					Psoriasis cohort	611 (562-663)	52	
							=1 case per 1923 pt/year	
Mehta 2011	MACE	HR 1.53 (1.26-1.85)			**Incidence per 1000 person-years (95% CI)**			
					Control: 11.6 (10.7-12.6)			
					Psoriasis: 16.4 (14.3-18.9)			
					Based on HR model:			

<table>
<tr><th>Study</th><th>Outcome</th><th>Relative risk estimate</th><th>Absolute risk estimate</th></tr>
<tr><td></td><td></td><td></td><td>Attributable risk for 10-year incidence of MACE = 6.2% (6.2 excess MACE per 1000 person years)
=1 excess event per 161 patients per year</td></tr>
<tr><td>Wakkee</td><td>Acute MI</td><td>HR 0.94 (0.80, 1.11)</td><td>Outcome | Incidence rate/100,000 person years | Excess risk/100,000 person years
Ref cohort | 235 (211-260) | -
Psoriasis cohort | 234 (201-262) | -1
= 1 fewer case per 100,000 pt/year</td></tr>
<tr><td>Gelfand 2006A</td><td>MI</td><td>Age | HR
Mild | Severe
30 | 1.29 (1.14 -1.46) | 3.10 (1.98-4.86)
60 | 1.08 (1.03-1.13) | 1.36 (1.13-1.64)</td><td>Incidence per 1000 person years
Control: 3.58 (3.52-3.65)
Mild psoriasis: 4.04 (3.88-4.21)
Severe psoriasis: 5.13 (4.22-6.17)

Age | Attributable risk/ 10,000 person years | Excess risk
Mild | Severe | Mild | Severe
30-40 | 1.068 | 7.222 | 1 MI per 9365 pt/year | 1 MI per 1385 pt/year
40-50 | 2.743 | 16.060 | 1 MI per 3646 pt/year | 1 MI per 623 pt/year
50-60 | 4.658 | 23.250 | 1 MI per 2147 pt/year | 1 MI per 430 pt/year</td></tr>
</table>

Study	Outcome	Relative risk estimate	Absolute risk estimate
Brauchli 2009A	**MI**	IRR All 1.07 (0.89-1.29) 0-29 years NA 30-59 years 1.99 (1.37-2.88) 60-80+ years 0.92 (0.75-1.14)	**IR per 1000 person-years (95% CI)** **ARD/1000 person years Excess risk** Psoriasis / Control All pts/year: 1.58 (1.39-1.79) / 1.47 (1.29-1.69); 0.11; 1 MI per 9091 Age 0-29: NA / 0.03 (0.00-0.15); -; - Age 30-59 pts/year: 1.08 (0.86-1.35) / 0.54 (0.39-0.75); 0.54; 1 MI per 1852 Age 60-80+ pts/year: 4.01 (3.44-4.68) / 4.35 (3.75-5.05); -0.34; -1 MI per 2941
Kaye2008	Myocardial infarction	1.21 (1.10-1.32)	Incident MI cases in the psoriasis and comparison cohorts **Incidence/1000 after 10 y follow-up** **Excess risk from psoriasis/1000** Psoriasis n=44164 Comparison n=219784 27.7 22.6 5.1 = 1 case per 1961 patients per year
Gelfand 2009	Stroke	**HR** **Mild:** 1.06 (1.01, 1.11) **Severe:** 1.43 (1.10, 1.87)	**Incidence of stroke in patients with psoriasis compared with control patients** **Mild group** **Severe group** **Variable** **Control (n=496,666)** **Psoriasis (n=129,143)** **Control (n=14,330)** **Psoriasis (n=3,603)** No of new stroke cases: 8,535 (1.72%) / 2,100 (1.63%) / 212 (1.48%) / 74 (2.05%) Incidence per 1,000 person-years (95% CI): 4.05 (3.96, 4.13) / 3.68 (3.52, 3.84) / 4.39 (3.82, 5.03) / 6.05 (4.76, 7.60)

Study	Outcome	Relative risk estimate	Absolute risk estimate
			Excess risk attributable to psoriasis 1 in 4115 per year and 1 in 530 per year for mild and severe disease (based on adjusted analysis)
Ahlehoff 2011E	Stroke	**Mild psoriasis** 1.25 (1.17-1.34) **Severe psoriasis** 1.65 (1.33-2.05)	**Event rates per 1000 observational years** **Control** 3.06 (Overall), 0.23 (<50), 5.94 (≥50) **Mild** 4.54 (Overall), 0.61 (<50), 6.74 (≥50) **Severe** 6.82 (Overall), 1.56 (<50), 8.88 (≥50) **Absolute risk difference - mild** 1.48 (Overall), 0.38 (<50), 0.8 (≥50) **Absolute risk difference - severe** 3.76 (Overall), 1.33 (<50), 2.94 (≥50) **Excess events overall = 1 in 676 patients per year for mild/ 1 in 266 patients per year for severe** **Attributable risk %:** Mild: 20.0% Severe: 39.4%
Brauchli 2009A	Stroke	IRR All 0.92 (0.77-1.09) 0-29 years NA 30-59 years 0.75 (0.49-1.16) 60-80+ years 0.98 (0.81-1.18)	**Age risk** / **IR per 1000 person-years (95% CI)** Psoriasis / Control / **ARD/1000 person years** / **Excess** All: 1.69 (1.50-1.90) / 1.84 (1.63-2.07) / 0.15 / 1 stroke per 6667 pts/year 0-29: 0.02 (0.00-0.14) / NA / - 30-59: 0.52 (0.37-0.71) / 0.69 (0.51-0.91) / -0.17 / -1 stroke per 5882 pts/year 60-80+: 5.10 (4.48-5.81) / 5.22 (4.58-5.94) / -0.12 / -1 stroke per 8333 pts/year
Brauchli 2009A	TIA	IRR All 0.98 (0.81-1.19) 0-29 years NA 30-59 years 1.14 (0.66-1.97)	**Age (years)** / IR per 1000 person-years (95% CI) Psoriasis / Control / ARD /1000 person years / Excess risk All: 1.31 (1.14-1.50) / 1.34 (1.16-1.54) / -0.03 / -1 TIA per 33,333 pts/year

Study	Outcome	Relative risk estimate	Absolute risk estimate
		60-80+ years 0.99 (0.80-1.22)	0-29 NA NA - - 30-59 0.39 (0.27-0.56) 0.34 (0.23-0.51) 0.05 1 TIA per 20,000 pts/years 60-80+ 4.00 (3.45-4.63) 4.04 (3.48-4.68) -0.04 -1 TIA per 25,000 pts/years
Ahlehoff 2011	VTE	**Adjusted IRR (95% CI)** **< 50 years** **≥ 50 years** Mild 1.24 (0.97-1.58) 1.26 (1.13-1.42) Severe 3.14 (1.98-4.97) 1.74 (1.32-2.28)	**Incidence rate per 1000 person years (95% CI)** **< 50 years** **≥ 50 years** Controls 0.58 (0.57-0.59) 2.03 (2.01-2.05) Mild 0.73 (0.56-0.95) 2.74 (2.4-3.06) Severe 2.10 (1.32-3.33) 3.93 (3.01-5.13) **Absolute risk difference vs control per 1000 person years** **< 50 years** **≥ 50 years** 0.15 (1 VTE per 6667 pts/yr) 0.71 (1 VTE per 1408 pts/yr) 1.52 (1 VTE per 658 pts/yr) 1.9 (1 VTE per 526 pts/yr)
CVD 'risk factors'			
Kaye2008	Diabetes	HR: 1.33 (1.25-1.42)	**Incident diabetes cases in the psoriasis and comparison cohorts** **Incidence/1000 after 10 y follow-up** **Excess risk from psoriasis/1000** **Psoriasis n=44164** **Comparison n=219784** 57.3 43.9 13.4 = 1 case per 746 patients per year
Brauchli 2008	Diabetes	**IRR (95% CI)** **All 1.36 (1.20-1.53)** 0-29 years 2.75 (1.24-6.13) 30-59 years 1.33 (1.09-1.61) 60-79 years 1.43 (1.21-1.69) 80+ years 1.12 (0.71-1.75)	**Age, years risk** **IR per 1000 person-years (95% CI)** **ARD/1000 person years** **Excess** **Psoriasis** **Control** Overall 4.06 (3.75-4.39) 2.98 (2.92-3.28) 1.08 1 case per 926 pts/year 0-29 pts/year 0.45 (0.28-0.71) 0.16 (0.07-0.35) 0.29 1 case per 3448 30-59 pts/year 3.38 (2.98-3.84) 2.55 (2.19-2.97) 0.83 1 case per 1205 60-79 8.92 (8.01-9.93) 6.22 (5.47-7.09) 2.7 1 case per 370 pts/year

Study	Outcome	Relative risk estimate	Absolute risk estimate
			80+ pts/year 5.87 (4.33-7.95) 5.24 (3.77-7.28) 0.63 1 case per 1587
Kaye2008	Hyperlipidaemia	1.17 (1.11-1.23)	**Incident hyperlipidaemia cases in the psoriasis and comparison cohorts** **Incidence/1000 after 10 y follow-up** **Excess risk from psoriasis/1000** **Psoriasis n=44164** **Comparison n=219784** 91.1 77.7 13.4 = 1 case per 746 patients per year
Kaye2008	Obesity	1.18 (1.14-1.23)	**Incident obesity cases in the psoriasis and comparison cohorts** *Obesity is defined as body mass index>/=30kgm^{-2} **Incidence/1000 after 10 y follow-up** **Excess risk from psoriasis/1000** **Psoriasis n=44164** **Comparison n=219784** 139.0 118.0 21 = 1 case per 476 patients per year
Kaye2008	Hypertension	1.09 (1.05-1.14)	**Incident hypertension cases in the psoriasis and comparison cohorts** **Incidence/1000 after 10 y follow-up** **Excess risk from psoriasis/1000** **Psoriasis n=44164** **Comparison n=219784** 138.5 129.4 9.1 = 1 case per 1099 patients per year

Q.7.2 Cancer

Study	Outcome	Relative risk estimate	Absolute risk estimate		
Gelfand 2003	Lymphoma – based on adjusted figures	IRR (adjusted) 2.94 (1.82-4.74)	**Variable** Incidence rate of lymphoma per 10000 person-years Attributable risk (excess no. of lymphoma cases related to psoriasis)	**Psoriasis** 18.3 122 /100000 per year *1 more per 820 pts/year*	**No psoriasis** 6.1 -
Gelfand 2006	Lymphoma – based on	HR 1.35 (1.17, 1.55)	**Attributable risk (excess no. of cases related to psoriasis)** **Lymphoma** 7.9/100,000 per year (1 more per 12,658 pts/year)		

Study	Outcome	Relative risk estimate	Absolute risk estimate
	adjusted figures	1.48 (1.05, 2.08) 4.34 (2.89, 6.52)	**HL** 1.8/100,000 per year (1 more per 55,556 pts/year) **TCL** 4.0/100,000 per year (1 more per 25,000 pts/year)
Prizment	Cancer	HR (95% CI) Any 1.1 (0.9-1.4) Breast 1.0 (0.7-1.5) Lung 1.3 (0.8-2.0) Colon 1.6 (1.0-2.4)	**Age-adjusted incidence rate per 1000** **Psoriasis** / **Control** / **Difference** Total 20.8 / 16.5 / 4.3 Breast 5.3 / 5.1 / 0.2 Lung 3.5 / 1.7 / 1.8 Colon 3.9 / 2.2 / 1.7 Note: follow-up was 2-15 years
Hannuksela-Svahn 2000	Cancer	**Primary site** / **SIR** / **95% CI** All sites 1.3 1.2-1.4 Mouth 0.7 0.0-3.6 Pharynx 1.3 0.3-3.9 Oesophagus 1.2 0.5-2.5 Stomach 1.1 0.8-1.5 Colon 0.9 0.5-1.3 Liver 1.9 0.9-3.3 Pancreas 1.5 1.0-2.2 Larynx 2.9 1.5-5.0 Lung, bronchus 1.5 1.2-1.8 Breast 0.9 0.6-1.2 Kidney and renal pelvis 0.8 0.4-1.4 Bladder, urethra, and urethra 1.4 0.9-2.1 Skin melanoma 0.8 0.3-1.6 Non-melanoma skin cancer 3.2 2.3-4.4 Nervous system 1.1 0.6-1.9 Non-Hodgkin's lymphoma 2.2 1.4-3.4 Hodgkin's disease 3.3 1.4-6.4	**Primary site per 1000 pts** / **Obs** / **Exp** / **Difference** / **Attributable risk** All sites 533 425.8 107.2 18.9 Mouth 1 1.6 -0.6 -0.1 Pharynx 3 2.2 0.8 0.1 Oesophagus 7 5.7 1.3 0.2 Stomach 34 30.8 3.2 0.6 Colon 20 23.5 -3.5 -0.6 Liver 11 5.9 5.1 0.9 Pancreas 26 17.2 8.8 1.5 Larynx 12 4.2 7.8 1.4 Lung, bronchus 101 68.0 33 5.8 Breast 37 43.4 -6.4 -1.1 Kidney and renal pelvis 12 15.1 -3.1 -0.5 Bladder, urethra, and urethra 25 17.8 7.2 1.3 Skin melanoma 8 10.3 -2.3 -0.4 Non-melanoma skin cancer 40 12.4 27.6 4.9 Nervous system 14 12.7 1.3 0.2 Non-Hodgkin's lymphoma 21 9.6 11.4 2.0 Hodgkin's disease 8 2.5 5.5 1.0

Study	Outcome	Relative risk estimate		Absolute risk estimate					
				Note: mean follow-up 14 years; 5687 people with psoriasis					
Brauchli 2009	Cancer	**Type**	**Overall IRR (95% CI)**		**IR/1,000 person years**				**Difference in IR**	**Excess risk**
					Control		Psoriasis			
		All cancer	1.13 (1.02-1.24)	All cancer	5.18	4.83-5.55	5.83	5.47-6.22	0.65	1 event per 1538 pts/year
		Lympho-hematopoietic malignancies	1.81 (1.35-2.42)	Lymphohematopoietic malignancies	0.41	0.32-0.53	0.75	0.63-0.90	0.34	1 event per 2941 pts/year
		Excluding CTCL	1.69 (1.25-2.27)	Lymphohematopoietic malignancies (excluding CTCL)	0.41	0.34-0.53	0.70	0.58-0.84	0.29	1 event per 3448 pts/year
		Lymphoma overall	1.76 (1.19-2.58)	CTCL	NA	NA	0.05	0.03-0.10	0.05	1 event per 20000 pts/year
		Lymphoma (excluding CTCL)	1.55 (1.03-2.31)	Lymphoma overall	0.24	0.17-0.33	0.42	0.33-0.54	0.18	1 event per 5556 pts/year
		Leukaemia/MD	1.89 (1.21-2.94)	Lymphoma (excluding CTCL)	0.24	0.17-0.33	0.37	0.29-0.48	0.13	1 event per 7692 pts/year
		Lung	0.79 (0.60-1.06)	Leukaemia/MD	0.17	0.12-0.25	0.33	0.25-0.43	0.16	1 event per 6250 pts/year
		Melanoma	0.83 (0.50-1.36)	Lung	0.67	0.55-0.82	0.53	0.43-0.66	-0.14	-1 event per 7143 pts/year
		Breast	1.04 (0.83-1.31)	Melanoma	0.22	0.16-0.31	0.18	0.13-0.26	-0.04	-1 event per 25000 pts/year
		Prostate	0.84 (0.63-1.12)	Breast	1.71	1.45-2.02	1.79	1.53-2.10	0.08	1 event per 12500 pts/year
		Digestive organs	1.40 (1.10-1.78)							
		Pancreas	2.20 (1.18-4.09)							
		Oesophagus	1.36 (0.72-2.54)							
		Colorectal	1.35 (0.97-1.90)							
		Others	1.14 (0.67-1.95)							
		Female genital organs	1.38 (0.91-2.11)							
		Bladder/kidney	1.25 (0.84-1.85)							
		Brain	1.30 (0.69-2.45)							
		Other cancers	1.23 (0.94-1.59)							
		Metastasis	0.81 (0.53-1.22)							

Study	Outcome	Relative risk estimate			Absolute risk estimate						
					Prostate	1.38	1.13-1.69	1.16	0.93-1.43	-0.22	-1 event per 4545 pts/year
					Digestive organs	0.71	0.59-0.86	1.00	0.86-1.17	0.29	1 event per 3448 pts/year
					Pancreas	0.08	0.05-0.14	0.18	0.12-0.25	0.1	1 event per 10000 pts/year
					Oesophagus	0.11	0.07-0.17	0.14	0.10-0.22	0.03	1 event per 33333 pts/year
					Colorectal	0.37	0.28-0.48	0.50	0.40-0.62	0.13	1 event per 7692 pts/year
					Others	0.16	0.11-0.24	0.18	0.13-0.26	0.02	1 event per 50000 pts/year
					Female genital organs	0.43	0.31-0.60	0.60	0.45-0.79	0.17	1 event per 5882 pts/year
					Bladder/kidney	0.29	0.21-0.39	0.36	0.28-0.46	0.07	1 event per 14286 pts/year
					Brain	0.11	0.07-0.17	0.14	0.09-0.21	0.03	1 event per 33333 pts/year
					Other cancers	0.65	0.53-0.79	0.79	0.67-0.94	0.14	1 event per 7143 pts/year
					Metastasis	0.32	0.24-0.42	0.26	0.19-0.35	-0.06	-1 event per 16667 pts/year
Frentz 1999	Cancer	**Site**	**SIR**	**95% CI**	**Site**		**Obs**	**Exp**	**Difference**	**Excess risk per 1000 pts**	
		All malignant neoplasms	1.40	1.21-1.51	All malignant neoplasms		795	566.1	228.9	33.1	
		Melanoma of skin	1.3	0.8-2.1	Melanoma of skin		16	12.1	3.9	0.6	
		Non-melanoma skin cancer	2.46	2.13-2.83	Non-melanoma skin cancer		196	79.6	116.4	16.9	
		Oral cavity	1.7	1.0-2.7	Oral cavity		19	11.0	8	1.2	
		Pharynx	2.9	1.3-5.8	Pharynx		8	2.7	5.3	0.8	
					Stomach		22	18.0	4	0.6	

Study	Outcome	Relative risk estimate			Absolute risk estimate				
		Stomach	1.2	0.8-1.8	Colon	60	46.8	13.2	1.9
		Colon	1.3	1.0-1.6	Rectum	24	25.8	-1.8	-0.3
		Rectum	0.9	0.6-1.4	Larynx	11	5.5	5.5	0.8
		Larynx	2.0	1.0-3.6	Lung	113	73.4	39.6	5.7
		Lung	1.5	1.3-1.9	Breast	54	46.8	7.2	1.0
		Breast	1.0	0.7-1.2	Kidney	18	15.3	2.7	0.4
		Kidney	1.2	0.7-1.9	Bladder	34	34.1	-0.1	0.0
		Bladder	1.0	0.7-1.4	Connective tissue	5	1.6	3.4	0.5
		Connective tissue	3.2	1.0-7.4	Non-Hodgkin's lymphoma	16	11.7	4.3	0.6
		Non-Hodgkin's lymphoma	1.4	0.8-2.2	Leukaemia	12	13.0	-1	33.1
		Leukaemia	0.9	0.5-1.6					

Q.7.3 Mortality

Study	Outcome	Relative risk estimate		Absolute risk estimate			
Abuabara	Mortality – various causes		**HR (95% CI)**	**Cause of death**	**Absolute risk/1000 person years**	**Excess risk/ person years**	**Excess risk**
		Diabetes	2.86 (1.08-7.59)	Diabetes	2.1	0.4	1 more death per 2500 pts/year
		Kidney disease	4.37 (2.24-8.53)	Kidney disease	3.5	1.2	1 more death per 833 pts/year
		Liver disease	2.03 (0.37-11.12)	Liver disease	0.8	0.1	1 more death per 10,000 pts/year
		Malignant neoplasms	1.41 (1.07-1.86)	Malignant neoplasms	39.0	1.6	1 more death per 625 pts/year

Study	Outcome	Relative risk estimate	Absolute risk estimate
Ahlehoff 2011B	All cause mortality	HR (95% CI) 1.18 (0.97-1.43)	**Incidence rate per 1000 person years (95% CI)** / **ARD/1000 person years** / **Excess risk in psoriasis** Psoriasis: 138.3 (114.1-167.7) Control: 119.4 (117.2-138.8) / 18.9 / 1 death per 53 pts/year
Gelfand 2007	All cause mortality	HR (95% CI) All psoriasis: 1.0 (0.99-1.04) mild psoriasis: 1.0 (0.97-1.02) severe psoriasis: 1.5 (1.3-1.7)	Incidence rate of mortality per 1000 person-years (95% CI) Control: 12.2 (12.0-12.3) Mild psoriasis: 12.0 (11.7-12.3) Difference = -0.2 (1 fewer deaths per 5000 pts per year) **Severe psoriasis (age and sex adjusted)** Age, years / Mortality rate per 1000 patient-years in control / AR, no. of deaths per 1000 patients-years / Excess risk, no. of exposed deaths All ages ≥18 / 12.0 / 6.0 / 1/166 patients per year 30-39 / 0.8 / 1.8 / 1/856 patients per year 40-49 / 2.0 / 2.3 / 1/440 patients per year 50-59 / 6.4 / 5.6 / 1/179 patients per year 60-69 / 20.1 / 12.9 / 1/78 patients per year 70-79 / 48.5 / 20.9 / 1/48 patients per year 80-89 / 106.7 / 26.7 / 1/38 patients per year

Q.7.4 Depression

Study	Outcome	Relative risk estimate	Absolute risk estimate
Kurd2010	**Depression**	**HR** **Mild:** 1.38 (1.35-1.40) **Severe**: 1.72 (1.5-1.88) **All**: 1.39 (1.37-1.41)	**Attributable risk of diagnosis of depression attributable to psoriasis adjusted for age and sex per 1000 person years** **Mild psoriasis** / **Severe psoriasis** / **All psoriasis** 11.5 / 25.5 / 11.8 =1 case for every 87 patients / =1 case for every 39 patients / =1 case for every 85 patients

Study	Outcome	Relative risk estimate	Absolute risk estimate		
			with psoriasis per year	with psoriasis per year	with psoriasis per year

Q.8 Biologics

Q.8.1 Sensitivity analysis: ustekinumab

One study for the comparison of ustekinumab in those with and without prior biologic exposure (section 20.2.4) included patients who had received overlap therapy with non-biologic systemic agents in the primary analysis. However, in the call for evidence data the numbers who had received overlap therapy were available and a sensitivity analysis was performed excluding these patients.

Of 80 who achieved PASI75 at week 16, 10 received overlap therapy during induction; 4 of these were still on an additional systemic therapy at 16 weeks. Additional therapies included: ciclosporin (n=5), methotrexate (n=4) and acitretin (n=1). Of these 10, 7 had previous biologic exposure and 3 were biologic naïve. Of the 47 patients who failed to achieve PASI75, 19 patients had additional systemic therapy (18 received treatment as overlap and 1 as rescue). Of the 19 patients 3 were biologic naïve, including the patient who received rescue therapy, and 16 had previous biologic exposure.

Please see evidence profile below.

Q.8.1.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ustekinumab in those with previous biologic	No previous biologic	Relative (95% CI)	Absolute	
PASI75 (week 16) - any biologic exposure vs none											
1 Laws 2011	observational studies	very serious[a]	no serious inconsistency	serious[b]	serious[c]	none	64/106 (60.4%)	16/21 (76.2%)	RR 0.79 (0.6 to 1.05)	160 fewer per 1000 (from 305 fewer to 38 more)	⊕OOO VERY LOW
PASI75 (week 16) - any biologic exposure vs none (overlap therapy responders removed)											

1 Laws 2011	observational studies	very serious[a]	no serious inconsistency	no serious indirectness[d]	serious[c]	none	57/83 (68.7%)	13/15 (86.7%)	RR 0.79 (0.62 to 1.01)	182 fewer per 1000 (from 329 fewer to 9 more)	⊕OOO VERY LOW

(a) Failure to adequately control for confounding (no matching for prognostic factors or adjustment in statistical analyses)

(b) Note: prior biologics included efalizumab (proportion unclear)

(c) 10/80 who achieved PASI75 at week 16 received overlap therapy (CSA, MTX or acitretin) during induction; 4 of these were still on an additional systemic therapy at 16 weeks. Of these 10, 7 had had previous biologic exposure and 3 were biologic naive. Also, prior biologics included efalizumab (proportion unclear).

(d) Confidence interval ranges from clinically important effect to no effect

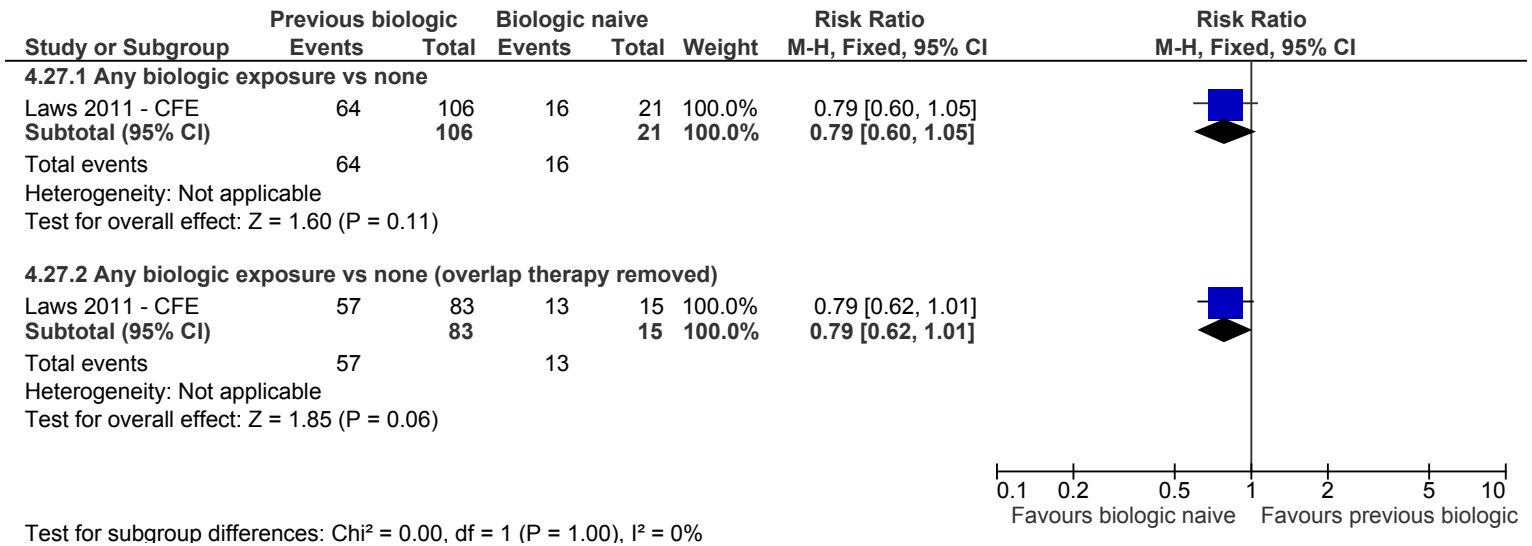
Q.8.1.2 Evidence statement

In people with psoriasis being treated with ustekinumab, there was no statistically significant difference between those with and without prior exposure to biologic therapy for:

- PASI75 (week 16) [1 study; 98 participants; very low quality evidence][92,93]

Q.8.1.3 Forest plot

Figure 357: PASI75 (week 16)



There was no notable difference between the effect estimate for the full sample and for the sample including only those receiving no concomitant therapy, although the response rates in both groups were higher when those requiring additional therapy were removed from the sample.

Q.10.1 Ustekinumab vs ustekinumab following failure of etanercept

These data were included in the original review presented to the GDG but were superseded by the evidence made available in the call for evidence, which are presented in sections 20.2.4, 20.5 and 20.6 and provide more direct evidence to address the review question. Note that in the data summarised below those who received ustekinumab in the first trial phase included 10.4% in whom this was not the first biologic.

Q.10.1.1 Evidence profile

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ustekinumab in those who failed etanercept	Ustekinumab	Relative (95% CI)	Absolute	
Clear/nearly clear (PASI90; 12 weeks)											
1 Griffiths 2010	randomised trials	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	12/50 (24%)	155/347 (44.7%)	RR 0.54 (0.32 to 0.89)	205 fewer per 1000 (from 49 fewer to 304 fewer)	⊕⊕OO LOW
Clear/nearly clear (PGA; 12 weeks)											
1 Griffiths 2010	randomised trials	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	20/50 (40%)	245/347 (70.6%)	RR 0.57 (0.4 to 0.8)	304 fewer per 1000 (from 141 fewer to 424 fewer)	⊕⊕OO LOW
PASI75 (12 weeks)											
1 Griffiths 2010	randomised trials	serious[a]	no serious inconsistency	serious[b]	no serious imprecision	none	24/50 (48%)	256/347 (73.8%)	RR 0.65 (0.48 to 0.87)	258 fewer per 1000 (from 96 fewer to 384 fewer)	⊕⊕OO LOW
Withdrawal due to toxicity											
1 Griffiths 2010	randomised trials	serious[a]	no serious inconsistency	serious[b]	very serious[c]	none	2/295 (0.68%)	4/347 (1.2%)	RR 0.59 (0.11 to 3.19)	5 fewer per 1000 (from 10 fewer to 25 more)	⊕OOO VERY LOW
Serious adverse events											
1 Griffiths 2010	randomised trials	serious[a]	no serious inconsistency	serious[b]	serious[d]	none	10/295 (3.4%)	4/347 (1.2%)	RR 2.94 (0.93 to 9.28)	22 more per 1000 (from 1 fewer to 95 more)	⊕OOO VERY LOW

(a) Unclear allocation concealment

(b) Not a direct comparison: data available for initial response in ustekinumab group and response among etanercept non-responders who crossover to ustekinumab during later phase of trial; selective outcome reporting: response rates following failure of initial therapy not given for all groups; 11.8% of those receiving etanercept initially and 10.4% of those receiving ustekinumab initially had previously received another biologic agent. Also, high dose of etanercept (50 mg twice weekly).

(c) Confidence interval crosses the boundary for clinical significance in favour of both groups, as well as line of no effect

(d) Confidence interval ranges from clinically important effect to no effect

Q.10.1.2 Evidence statements

In people with psoriasis, ustekinumab 90 mg in the first trial phase was statistically significantly better than ustekinumab 90 mg following failure of etanercept for:

- Clear or nearly clear (PASI90 or PGA; 12 weeks) [1 study; 397 participants; low quality evidence][94]
- PASI75 (12 weeks) [1 study; 397 participants; low quality evidence][94]

Note: even in these cases where those using ustekinumab in the first trial phase had a statistically significantly better result, those who had previously failed etanercept still had substantial response rates (24% PASI90; 40% clear/nearly clear PGA; 48% PASI75).

In people with psoriasis, there was no statistically significant difference between ustekinumab 90 mg following failure of etanercept and ustekinumab 90 mg in the first trial phase for:

- Withdrawal due to toxicity (12 weeks) [1 study; 642 participants; very low quality evidence][94]
- Serious adverse events (12 weeks) [1 study; 642 participants; very low quality evidence][94]

Forest plots

Figure 358: Clear/nearly clear (PASI90; week 12)

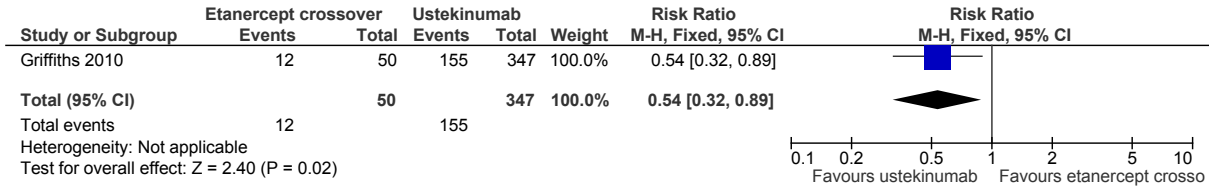


Figure 359: Clear/nearly clear (PGA; week 12)

Study or Subgroup	Etanercept crossover Events	Total	Ustekinumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Griffiths 2010	20	50	245	347	100.0%	0.57 [0.40, 0.80]
Total (95% CI)		**50**		**347**	**100.0%**	**0.57 [0.40, 0.80]**
Total events	20		245			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.22 (P = 0.001)

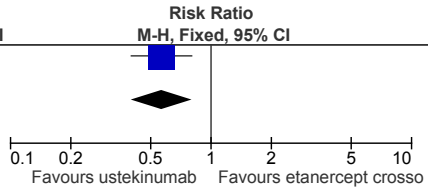


Figure 360: PASI75 (week 12)

Study or Subgroup	Etanercept crossover Events	Total	Ustekinumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Griffiths 2010	24	50	256	347	100.0%	0.65 [0.48, 0.87]
Total (95% CI)		**50**		**347**	**100.0%**	**0.65 [0.48, 0.87]**
Total events	24		256			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.85 (P = 0.004)

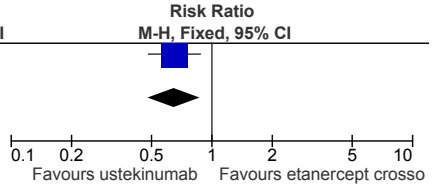


Figure 361: Withdrawal due to toxicity

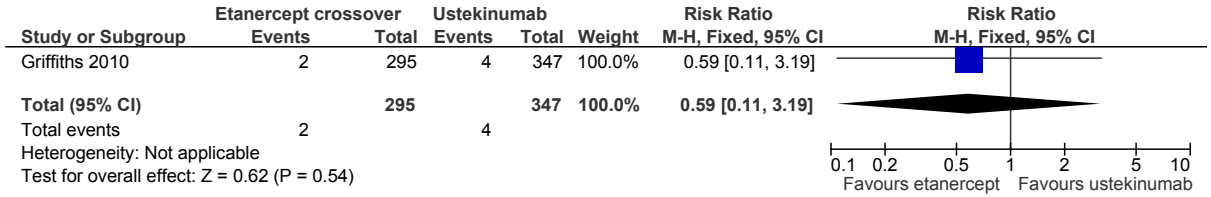
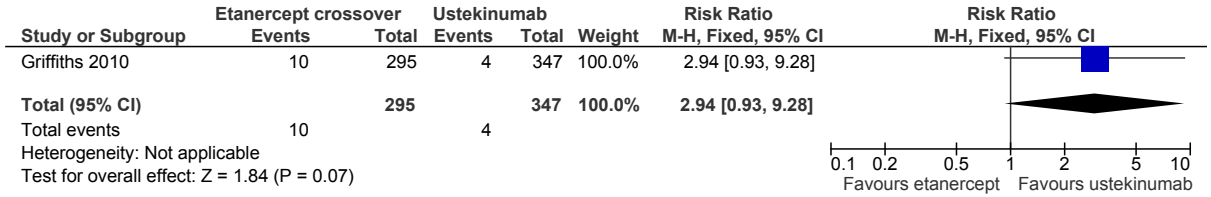


Figure 362: Serious adverse events



Appendix R: Future research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

R.1 Key future research recommendations (FRR)

R.1.1 FRR1 Assessment of disease severity and impact

In children, young people and adults with psoriasis, can tools be developed and/or existing ones further refined and validated to:

- assess disease severity and impact in both non-specialist and specialist healthcare settings, to facilitate assessment, appropriate referral, treatment planning and measurement of outcomes
- measure burden and cumulative effect of disease activity, severity and impact for people with both psoriasis and psoriatic arthritis?

Why this is important:

Assessment of disease severity and impact is fundamental to delivering high-quality health care and measuring outcomes. The evidence review indicates that the existing tools have important limitations, and have not been validated in relevant healthcare settings or in children or young people. Future research should ensure that tools are developed that capture information on site of involvement as well as extent and the impact of previous treatments. Tools should capture all aspects of impact on life including physical, psychological and social wellbeing and factors that may influence this impact, such as distress and beliefs about psoriasis. Tools that can be used by patients (as well as healthcare professionals) to assess disease severity and that encompass new technologies should be evaluated to facilitate, when appropriate, modern healthcare delivery models (for example, remote monitoring of disease activity).

In addition, understanding the true burden and effect of disease activity, severity and impact for both psoriasis and psoriatic arthritis has not previously been comprehensively studied. Capturing this information and distilling out significant factors for focused investigation will lead to better understanding of the needs of this particular group of people and the impact of treatments that benefit both disease compartments (skin and joints).

Table 63: Criteria for selecting high-priority research recommendations:

Criterion	Explanation
Importance to patients or the population	Assessment of disease severity and impact is fundamental to delivering high-quality health care and measuring outcomes Separate focus of burden of disease for a subset of the above point 1 – for people with both psoriasis and psoriatic arthritis
Relevance to NICE guidance	Results would inform recommendations for assessment methods in future updates of the guideline
Relevance to the NHS	Highly relevant to the NHS to ensure appropriate referral, treatment planning, evaluation of interventions and effective targeting of resources
Study design	The study should include a sufficient sample size. Tools that capture information on site of involvement as well as extent, and the impact of previous treatments are of particular interest, as well as tools that capture all aspects of impact on life including physical, psychological and social wellbeing and factors that may influence this impact, such as distress and beliefs about psoriasis. In addition, tools

Criterion	Explanation
	that can be used by patients (as well as healthcare professionals) to assess disease severity and that encompass new technologies should be evaluated to facilitate, when appropriate, modern healthcare delivery models (for example, remote monitoring of disease activity).
National priorities	No
Current evidence base	No evidence was found for the use of the tools in children, in primary care settings or specifically for different psoriasis phenotypes or in people with both skin and joint disease. The evidence review indicates that the existing tools have important limitations, and have not been validated in relevant healthcare settings In addition, understanding the true burden and effect of disease activity, severity and impact for both psoriasis and psoriatic arthritis has not previously been comprehensively studied.
Equality	Research should include children, young people and older people
Feasibility	No known feasibility issues
Other comments	Elements of this future research recommendation may include, from a psychological perspective, exploring: Depression Distress Mood Coping This is not an exhaustive list and provides suggestions that researchers may wish to expand upon when presenting detailed research protocols.

R.1.2 FRR2 Methotrexate and risk of hepatotoxicity

What is the impact of methotrexate compared with other approaches to care (for example other systemic non-biological or biological treatments) on risk of significant liver disease in people with psoriasis and do risk factors such as obesity, alcohol use or diabetes alter this risk?

Why this is important:

The evidence review indicates that people with psoriasis may be at risk of liver disease, and there is great uncertainty about the contributing role of methotrexate. Clinician and patient concerns about this side effect are a common cause of treatment discontinuation. However, existing studies are poorly controlled for important confounders and many are very old. Methotrexate is a low cost intervention that is effective in an important proportion of patients. Research in this area will properly delineate the size of risk and how to minimise it. Future research should be adequately powered to detect clinically relevant liver disease, use relevant tools to do so, and properly control for relevant confounders.

Table 64: Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	Methotrexate is a commonly prescribed drug in psoriasis and psoriatic arthritis. It is also used as co-therapy with TNF-antagonists to improve efficacy. People with psoriasis may be at risk of liver disease, and there is great uncertainty about the contributing role of methotrexate.
Relevance to NICE guidance	Outcomes will inform future NICE guidance. At present there may be a reluctance in clinical practice to use methotrexate in people with psoriasis who have risk factors and/or reluctance to continue methotrexate with high cumulative doses (>3g). However, there is not robust evidence to underpin this view.

Criterion	Explanation
Relevance to the NHS	The insidious development of liver fibrosis and ultimately cirrhosis is of great clinical concern given this may be irreversible, and of very significant impact. Research in this area will properly delineate the size of risk and how to minimise it.
Study design	Large, prospective cohort study of people with psoriasis receiving methotrexate compared with those receiving other interventions in a sample group matched for disease severity. Research in this area would need to involve large numbers of patients given that the absolute risk of liver fibrosis may be low, control properly for confounders (obesity, diabetes, alcohol), and use relevant tools (including standardised histology grading scales) and validated outcomes. Follow up should be long term. Details should include whether liver pathology was present prior to MTX administration.
National priorities	Nil
Current evidence base	Existing studies are small, inadequately controlled for important confounders, report insufficient data and many are very old.
Equality	This research recommendation will include all relevant groups
Feasibility	Long term follow up may be difficult
Other comments	None

R.1.3 FRR3 Rapid escalation to systemic treatments

In people with psoriasis, does early intervention with systemic treatments improve the long-term prognosis of psoriasis severity, comorbidities (including psoriatic arthritis), or treatment-related adverse effects, and are there any clinical (for example demographic or phenotypic) or laboratory (for example genetic or immune) biomarkers that can be used to identify those most likely to benefit from this treatment approach?

Why this is important:

At present the treatment pathway for people with psoriasis follows clinical need as no studies have been conducted to evaluate whether early intervention with systemic treatments alters prognosis. Consequently, patients with more severe disease sequence through all therapies in the treatment pathway, with a proportion requiring high-cost biological interventions to maintain disease control. The evidence indicates that there are very few treatment options for people with chronic disease, all of them are associated with side effects, many are co-dependent (for example escalated risk of skin cancer in people treated with the phototherapy and ciclosporin sequence), and loss of response to biological therapies is a significant clinical issue. If early intervention with systemic treatments was shown to alter the prognosis, particularly if there were markers that could stratify those likely to benefit, this would be of major importance to patients, and likely to deliver much more cost-effective treatment strategies.

Table 65: Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	The current treatment pathway for people with psoriasis requires those with more severe disease to sequence through all therapies in the treatment pathway. The findings of this study could mean that people with more severe disease are able to receive more appropriate interventions earlier in the treatment pathway, and so achieve satisfactory disease control, sooner with exposure to fewer interventions. This could improve prognosis, quality of life and adverse event risk.
Relevance to NICE guidance	Future NICE guidance may recommend more intensive and earlier up stream treatment for those people with psoriasis.

Criterion	Explanation
Relevance to the NHS	Potential for delivering more cost effective treatment strategies.
Study design	Prospective cohort study with long-term follow-up comparing early intervention with current standard care. Multivariable regression analysis accounting for time and controlling for all relevant confounders should be performed. It would be important to a priori specify subgroup analysis for those with mild and severe psoriasis, if possible using psoriasis severity assessment tools rather than surrogate markers of severity.
National priorities	Improved quality of life for those living with psoriasis which may reduce work loss. Potentially this may reduce both chronic worklessness due to psoriasis and also short term work absence due to flares.
Current evidence base	Extremely limited
Equality	This research question has no particular equality issues.
Feasibility	This research should probably take place in a specialist environment (secondary care)
Other comments	None

R.1.4 FRR4 Self-management

Do structured psoriasis-focussed self-management programmes improve patient confidence, wellbeing and disease control compared with standard care?

Why this is important:

Virtually all patients self-manage their condition to a greater or lesser extent and this involves complex topical applications as well as systemic therapies to be used over many years in response to fluctuating disease severity. The evidence indicates that in contrast to many chronic disorders, there are no validated programmes to help patients achieve effective self-management. Establishing a focussed programme that effectively improves outcomes for patients would be of clinical benefit and likely deliver healthcare savings.

Table 66: Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	Results would inform national recommendations regarding specific factors that are important for self-management. All patients living with a long-term condition self-manage to a greater or lesser degree. Simply telling the person why or showing them how may not be enough to ensure it happens, information provision alone does not change behaviour. A well-designed programme will allow those living with psoriasis to make the most appropriate use of treatment options and fully engage with their treatment plan.
Relevance to NICE guidance	Future NICE guidance would be able to address self-management recommendations for psoriasis.
Relevance to the NHS	Access to self-management support may reduce the need for service use. Clinically the degree of effective self-management in order to optimise clinical outcomes is of interest.
Study design	Quantitative: Adequately powered, cluster randomised study with moderate to long term follow up Qualitative: Exploring and understanding the beliefs and perceptions of people with a long term condition such as psoriasis utilising a qualitative paradigm for example grounded theory and / or phenomenology

Criterion	Explanation
National priorities	Self-care and self-management are central to UK health policy on managing long-term conditions
Current evidence base	There is a paucity of evidence, only four RCTs were found all of which had methodological limitations. There was no direct evidence for concordance with treatment, distress, anxiety, depression or stress. No studies were available that assessed self-management exclusively in children with psoriasis. From a qualitative research perspective no grounded theory or phenomenological studies exploring the self-management concepts in people with psoriasis were found.
Equality	Children, younger people and older people should be included in future research on self-management
Feasibility	Teasing out the specific factors that are important for self-management may be difficult. Elements may potentially include: i) education; ii) information provision; iii) strategies for behaviour change; vi) psychological interventions; v) stepped care; vi) exercise; vii) adherence. Distilling out factors that successfully contribute to helping people self-manage psoriasis needs careful exploration.
Other comments	Self-management education programmes are distinct from patient education or skills training, in that they are designed to encourage people with long-term conditions to take a more active part in the management of their own condition. In addition, in relation to self-management, educational programmes should be distinguished from psychological interventions.

R.1.5 FRR5 Topical therapy

In people of all ages with psoriasis:

1. How should topical therapies be used to maintain disease control i) safely; ii) effectively and iii) what are the health economic implications?
2. What are the risks of 'real life' long term corticosteroid use, are there particular people at risk and what strategies can be used to modify or avoid risks?

Why this is important:

Currently, topical therapies, in some form or another, are prescribed to virtually everyone with psoriasis, often as first line psoriasis treatment and they are also frequently used adjunctively with other interventions. There is a wide array of potential topical agents available and further research specifically targeting therapeutic strategies together with sequencing of topical agents for maintaining disease control in the long term continues to deserve focused attention. In addition exploration of the risks associated with long term corticosteroid use and strategies aimed at modifying risk would be a critical element of this research to fill the current gap in the literature.

Table 67: Criteria for selecting high-priority research recommendations

Criterion	Explanation
Importance to patients or the population	The majority of people with psoriasis have localised disease; the importance of understanding topical maintenance treatments and the 'real life' long term risks are key to this research (for example steroid atrophy)
Relevance to NICE guidance	Future NICE guidance on topical therapy may change as a result of further information about the effectiveness and long term risks. This may impact across a wide array of long term dermatological conditions.
Relevance to the NHS	Potential for delivering further information pertaining to efficacy, safety and cost effectiveness of topical treatment strategies.
Study design	Multicentre adequately powered RCT

Criterion	Explanation
National priorities	For most people with psoriasis, topical treatments are prescribed for home-use to self-manage psoriasis. Variable outcomes are reported with the use of topical therapies and much of this variation is likely to relate to adherence. Adherence to treatment and the health economic implications of this are of national interest for long term conditions.
Current evidence base	Limited. The GDG noted there were no studies with appropriate comparators that addressed maintenance.
Equality	The GDG commented on the lack of evidence for the treatment of children with psoriasis especially at difficult to treat sites.
Feasibility	Highly feasible
Other comments	None

R.2 Other future research recommendations:

1. What is the validity and accuracy of existing and future screening instruments for PsA in dermatology and primary care settings?
2. What is the efficacy of the ASAS criteria for identifying inflammatory back pain in a psoriasis population?
3. Does treating psoriasis modify the risk of cardiovascular disease and are there any clinical (for example, demographic or phenotypic) or laboratory (for example genetic or immune) markers that identify those most likely to benefit?
3. What is the natural history of psoriatic arthritis and are there any adverse prognostic markers that identify individuals at risk of severe/aggressive/destructive disease?
4. Does reduction of relevant, modifiable cardiovascular risk factors (for example weight loss, exercise or statins) improve psoriasis and are there particular demographic, phenotypic or other biomarkers (for example age or disease severity) that identify those most likely to benefit?
5. What is the natural history of psoriasis and are there any adverse prognostic markers that identify individuals at risk of severe recalcitrant disease who might benefit from early intervention?
6. How does the documented increased risk of CVD/CVD risk factors among people with psoriasis compare to that observed with other chronic diseases?
7. What are the risks and benefits of proactively 'screening' the psoriasis population for co-morbidities?
8. What are the efficacy, safety and cost effectiveness of NBUVB compared to oral/topical PUVA in the treatment of palmoplantar pustulosis?
9. What are the long term risks (for example skin cancer and ageing) of NBUVB, are there any individuals at particular risk and what strategies can be used to modify or avoid these risks?
10. In people with psoriasis, what is the clinical effectiveness, safety, tolerability and cost effectiveness of NBUVB phototherapy and acitretin versus acitretin and placebo?
11. In people with psoriasis, when inducing remission, what are the clinical effectiveness (including duration of remission and psychological benefit), cost effectiveness, safety, tolerability and patient acceptability of complex topical therapies with or without NBUVB compared to a short course of systemic therapy (for example, ciclosporin)?
12. What is the risk of skin cancer in people with psoriasis exposed to phototherapy, systemic (including biological) therapies and are there any strategies that can modify or avoid this risk?
13. In people with psoriasis, are there any clinical (for example, demographic or phenotypic) or laboratory (for example genetic or immune) markers that identify people who will respond to

treatment with, or who will remain in remission following, treatment with methotrexate or ciclosporin?

14. In people with psoriasis, including pustular forms, what is the efficacy, optimal dosing, safety and cost-effectiveness of systemic non-biological agents for maintenance therapy (moderate to long-term outcomes are important)?
15. What is the most effective, safe and cost effective methotrexate dosing regimen to treat psoriasis and what is the role of folic acid in reducing efficacy or improving safety of methotrexate?
16. In children with psoriasis, what are the clinical effectiveness, safety, tolerability and cost effectiveness of methotrexate, ciclosporin and acitretin?
17. In people with palmoplantar pustulosis, what are the clinical effectiveness, safety, tolerability and cost effectiveness of acitretin and methotrexate?
18. What is the clinical utility and validity of non-invasive markers of liver fibrosis (for example, FibroScan, FibroTest and ultrasound) in people with psoriasis receiving methotrexate or other treatment interventions?
19. In people with psoriasis being treated with systemic non-biological or biological therapies what clinical or other markers predict optimal treatment outcomes?
20. Does a psoriasis-specific cognitive behavioural therapy intervention improve distress, quality of life and psoriasis severity compared with standard care?

Appendix S: Information to facilitate discussion of risks and benefits of treatments for people with psoriasis

Data are provided for the proportions of people achieving remission, withdrawing due to adverse events and experiencing specific adverse events (as rioritised by the GDG) for interventions that have been recommended in this guideline. Data are based on pooled estimates where possible and from trials with populations and dosing appropriate to the intervention. For full details of the duration of treatment and dosing schedules please refer to the main text of the guideline.

Text is in grey when the GDG had very low confidence in the absolute estimates, for example due to confounding and inadequate sample size.

S.1 Topical therapies (short term)

Intervention	**Population – psoriasis phenotype**	**N achieving remission (clear/nearly clear or PASI75)**			**N experiencing:**					
					Withdrawal due to drug toxicity			**Serious/named adverse events**		
		Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator†
Vitamin D or vitamin D analogues	Chronic plaque psoriasis of trunk and limbs	OD: 220/1000 BD: 487/1000	OD: 76/1000 BD: 122/1000	-	OD or BD: 23/1000	OD or BD: 29/1000	-	**Skin atrophy** BD: 1.9/1000	**Skin atrophy** BD: 3.2/1000	-
	Children with chronic plaque psoriasis of trunk and limbs	BD:605/1000	BD:441/1000	-	NA	NA	-	NA	NA	NA
	Scalp psoriasis	OD: 387/1000	OD: 219/1000	-	OD: 81/1000	OD: 52/1000	-	NA	NA	NA
Potent corticosteroids	Chronic plaque psoriasis of trunk and limbs	OD or BD: 394/1000	OD or BD: 77/1000	-	OD: 10/1000	OD: 79/1000 BD: 0/1000	-	**Skin atrophy**	**Skin atrophy**	-

Intervention	Population – psoriasis phenotype	N achieving remission (clear/nearly clear or PASI75)			N experiencing:					
					Withdrawal due to drug toxicity			Serious/named adverse events		
		Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator†
					BD: 25/1000			OD or BD: 5.5/1000	OD or BD: 0/1000	
	Scalp psoriasis	OD or BD: 632/1000	OD or BD: 223/1000	-	OD or BD: 9.5/1000	OD or BD: 41/1000	-	NA	NA	NA
Vitamin D or analogue and potent steroid, applied one in the morning and one in the evening	Chronic plaque psoriasis of trunk and limbs	611/1000	NA	Calcipotriol BD 469/1000	13/1000	NA	Calcipotriol BD: 26/1000	NA	NA	NA
Combined vitamin D or analogue and potent steroid	Chronic plaque psoriasis of trunk and limbs	OD: 494/1000	NA	Vit D OD: 193/1000	OD: 7.5/1000	NA	Vit D OD or BD: 27/1000	**Skin atrophy** OD: 4.2/1000	NA	**Skin atrophy** Vit D BD: 1.8/1000
	Scalp psoriasis	OD: 800/1000	OD: 500/1000	-	OD: 17/1000	OD: 0/1000	-	NA	NA	-
Very potent corticosteroids	Chronic plaque psoriasis of trunk and limbs	OD or BD: 625/1000	OD or BD: 13/1000	-	OD or BD: 4.6/1000	OD or BD: 6.0/1000	-	**Skin atrophy** OD or BD: 23/1000	**Skin atrophy** OD or BD: 0/1000	-
	Scalp psoriasis	OD or BD: 646/1000	OD or BD: 80/1000	-	OD or BD: 0/1000	OD or BD: 5.9/1000	-	**Skin atrophy**	**Skin atrophy**	-

Intervention	Population – psoriasis phenotype	N achieving remission (clear/nearly clear or PASI75)			N experiencing:					
					Withdrawal due to drug toxicity			Serious/named adverse events		
		Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator†
								OD or BD: 0/1000	OD or BD: 11/1000	
Tazarotene	Chronic plaque psoriasis of trunk and limbs	OD: 58/1000	OD: 20/1000	-	OD: 107/1000	OD: 44/1000	-	**Skin atrophy**: OD: 0/1000	**Skin atrophy** OD: 0/1000	-
Short-contact dithranol*	Chronic plaque psoriasis of trunk and limbs	OD: 430/1000	NA	Calcipotriol BD: 588/1000	OD: 82/1000	NA	Calcipotriol BD: 39/1000	NA	NA	NA
Coal tar	Chronic plaque psoriasis of trunk and limbs	OD or BD: 111/1000 to 519/1000 depending on formulation and follow-up	NA	Calcipotriol BD: 214/1000 to 723/1000 depending on follow-up	OD or BD: 0-56/1000 depending on formulation and follow-up	NA	Calcipotriol BD: 0-40/1000 depending on follow-up	NA	NA	NA
Tacrolimus	Psoriasis of the face and flexures	BD: 652/1000	BD: 309/1000	-	BD: 0/1000	BD: 25/1000	-	NA	NA	-
Pimecrolimus	Psoriasis of the flexures	BD: 714/1000	BD: 207/1000	-	BD: 0/1000	BD: 0/1000	-	**Skin atrophy** BD: 0/1000	**Skin atrophy** BD: 0/1000	-

† An active comparator will only be included if no placebo comparison is available; the standard intervention will be chosen if multiple active comparators are available

NA: Not available

-: Active comparison not reported as placebo comparison was available

**2/3 studies reported home-use of dithranol and in 1/3 studies the setting was unclear*

OD: Once daily

BD: Twice daily

S.2 Phototherapy (short-term)

Intervention	Population – psoriasis phenotype	N achieving remission (clear/nearly clear or PASI75)			N experiencing:					
					Withdrawal due to drug toxicity			Serious/named adverse events		
		Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator†
NBUVB vs PUVA	Plaque psoriasis	Twice weekly 647/1000	NA	Oral PUVA (twice weekly) 915/1000	Twice weekly 38/1000	NA	Oral PUVA (twice weekly) 47/1000	NA	NA	NA
PUVA (oral)	Palmoplantar pustulosis	3-4 times weekly 941/1000	No treatment 500/1000	-	3-4 times weekly 29/1000	No treatment 0/1000	-	**Burn** 3-4 times weekly 147/1000	**Burn** No treatment 0/1000	-
PUVA (cream)	Palmoplantar pustulosis	3 times weekly 952/1000	NA	NBUVB 3 times weekly 429/1000	3 times weekly 45/1000	NA	NBUVB 3 times weekly 0/1000	NA	NA	NA
NBUVB + vitamin D or analogues	Plaque psoriasis	3 times weekly UV plus BD topical 900/1000	NA	3 times weekly NBUVB alone 611/1000	3 times weekly UV plus BD topical 50/1000	NA	3 times weekly NBUVB alone 28/1000	**Burn** 3 times weekly UV plus BD topical 200/1000	NA	**Burn** 3 times weekly NBUVB alone 111/1000
BBUVB + vitamin D or analogues	Plaque psoriasis	Up to 3 times weekly UV plus BD topical 8 weeks	NA	BBUVB alone up to 3 times weekly 208/1000	Up to 3 times weekly UV plus BD topical 41/1000	NA	BBUVB alone up to 3 times weekly 19/1000	NA	NA	NA

Intervention	Population – psoriasis phenotype	N achieving remission (clear/nearly clear or PASI75)			N experiencing:					
					Withdrawal due to drug toxicity			Serious/named adverse events		
		Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator †	Intervention	Placebo	Active comparator†
		449/1000								
Liquor carbonic distillate (equivalent 2.3% coal tar) plus NBUVB	Plaque psoriasis	Clear (3 times weekly UV plus BD topical) 583/1000	NA	3 times weekly NBUVB alone 500/1000	3 times weekly UV plus BD topical 0/1000	NA	3 times weekly NBUVB alone 0/1000	**Burn** 3 times weekly UV plus BD topical 167/1000	NA	**Burn** 3 times weekly NBUVB alone 167/1000
Dithranol plus BBUVB	Psoriasis	3 times weekly UV plus BD topical 625/1000	NA	3 times weekly BBUVB alone 458/1000	NA	NA	NA	NA	NA	NA

† An active comparator will only be included if no placebo comparison is available; the standard intervention will be chosen if multiple active comparators are available

NA: Not available

-: Active comparison not reported as placebo comparison was available

BBUVB: Broadband UVB

NBUVB: Narrow band UVB

PUVA: Psoralen plus UVA

S.3 Systemic, non-biologic therapies (short term)

Intervention	Population – psoriasis phenotype	N achieving remission (clear/nearly clear or PASI75)		N experiencing:			
				Withdrawal due to drug toxicity		Serious/named adverse events	
		Intervention	Placebo	Intervention	Placebo	Intervention	Placebo
Methotrexate; incremental dosing (+folic acid)	Chronic plaque psoriasis	415/1000	188/1000	55/1000	20/1000	**Elevated liver enzymes (>1.5-2.5 ULN)** 91/1000	**Elevated liver enzymes (>1.5-2.5 ULN)** 75/1000
Ciclosporin	Chronic plaque psoriasis	2.5-3 mg 232/1000 5 mg 600/1000	44/1000	0/1000	0/1000	**Hypertension** 391/1000 **Decrease in GFR >15%** 3 mg/kg: 333/1000 5 mg/kg: 500/1000	**Hypertension** 333/1000 **Decrease in GFR >15%** 0/1000
	Palmoplantar pustulosis	652/1000	200/1000	NA	NA	**Hypertension** 37/1000	**Hypertension** 0/1000
Acitretin – 25 mg	Plaque, pustular and erythrodermic psoriasis	480/1000	188/1000	18/1000	0/1000	**Cheilitis** 850/1000 **Hair loss** 150/1000 **Elevated liver enzymes (>ULN)** 200/1000 **Elevated cholesterol (>ULN)** 0/1000	**Cheilitis** 300/1000 **Hair loss** 100/1000 **Elevated liver enzymes (>ULN)** 0/1000 **Elevated cholesterol (>ULN)** 53/1000

GFR: Glomerular filtration rate

NA: Not available

ULN: Upper limit of normal

S.4 Systemic, biologic therapies (short term)

Intervention	Population – psoriasis phenotype	Prior biologics received	N achieving remission (clear/nearly clear or PASI75)			N experiencing: Withdrawal due to drug toxicity or serious adverse events		
			Intervention	Placebo	Active comparator†	Intervention	Placebo	Active comparator†
Infliximab	Adults with severe plaque psoriasis and prior biologic exposure	Unclear	723/1000	0/1000	-	NA	NA	NA
Etanercept	Adults with severe plaque psoriasis and prior biologic exposure	Included etanercept, infliximab, and adalimumab (proportions unclear)	370/1000	NA	Ustekinumab 556/1000	NA	NA	NA
Ustekinumab	Adults with severe plaque psoriasis and prior biologic exposure	Included etanercept, infliximab, and adalimumab (proportions unclear)	619/1000	170/1000	-	NA	NA	NA
Adalimumab	Adults with severe plaque psoriasis	Etanercept (32.1%), alefacept (23.1%), ustekinumab (23.1%), efalizumab (21.8%), infliximab (20.5%), and other (17.9%)	654/1000	NA	No prior biologic 744/1000	NA	NA	NA

† An active comparator will only be included if no placebo comparison is available; the standard intervention will be chosen if multiple active comparators are available

NA: Not available

-: Active comparison not reported as placebo comparison was available

S.5 Long-term risks

Intervention	Outcome(s)	Population – psoriasis phenotype	Number experiencing event
PUVA (oral)	Skin cancer – SCC	Plaque (84%), guttate (12%) and erythrodermic (4%) psoriasis	**Relative risk compared with the general population** **PUVA exposures RR** <100 5.1 (3.5-7.2) 100-159 8.4 (5.6-12.1) 160-336 26.5 (22.2-31.4) ≥337 68.5 (54.9-84.5) **Absolute increase in risk** **PUVA exposures SCCs % increase in 10-year risk** <100 18 **1.7%** 100-159 15 **2.7%** 160-336 68 **8.8 %** ≥337 34 **12.7%**
NBUVB	Skin cancer	Insufficient data available	
Methotrexate	Liver fibrosis, bone marrow suppression and pneumonitis	No long-term data available	
Ciclosporin	Hypertension, renal impairment, gout and hyperuricaemia	No long-term data available	
Acitretin	Hyperlipidaemia, hepatotoxicity, skeletal AEs and cheilitis	No long-term data available	

PUVA: Psoralen plus UVA

RR: Relative risk

SCC: Squamous cell carcinoma

Appendix T: Psoriasis Epidemiology Screening Tool (PEST)

Psoriasis Epidemiology Screening Tool (PEST)

PEST questionnaire *Score 1 point for each question answered in the affirmative. A total score of 3 or more is indicative of psoriatic arthritis*		
Question	**Yes**	**No**
1. Have you ever had a swollen joint (or joints)?		
2. Has a doctor ever told you that you have arthritis?		
3. Do your finger nails or toenails have holes or pits?		
4. Have you had pain in your heel?		
5. Have you had a finger or toe that was completely swollen and painful for no apparent reason?		

Source: G. H. Ibrahim, M. H. Buch, C. Lawson, R. Waxman, and P. S. Helliwell. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin.Exp.Rheumatol. 27 (3):469-474, 2009.

Appendix U:References for Appendices J - T

1 Oranje AP, Marcoux D, Svensson A, Prendiville J, Krafchik B, Toole J et al. Topical calcipotriol in childhood psoriasis. Journal of the American Academy of Dermatology. 1997; 36(2:Pt 1):203-208

2 Molin L, Cutler TP, Helander I, Nyfors B, Downes N. Comparative efficacy of calcipotriol (MC903) cream and betamethasone 17-valerate cream in the treatment of chronic plaque psoriasis. A randomized, double-blind, parallel group multicentre study. Calcipotriol Study Group. British Journal of Dermatology. 1997; 136(1):89-93

3 Kragballe K, Gjertsen BT, de HD, Karlsmark T, van de Kerkhof PC, Larko O et al. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. Lancet. 1991; 337(8735):193-196

4 Highton A, Quell J. Calcipotriene ointment 0.005% for psoriasis: a safety and efficacy study. Calcipotriene Study Group. Journal of the American Academy of Dermatology. 1995; 32(1):67-72

5 Dubertret L, Wallach D, Souteyrand P, Perussel M, Kalis B, Meynadier J et al. Efficacy and safety of calcipotriol (MC 903) ointment in psoriasis vulgaris. A randomized, double-blind, right/left comparative, vehicle-controlled study. Journal of the American Academy of Dermatology. 1992; 27(6 Pt 1):983-988

6 Harrington CI, Goldin D, Lovell CR, van de Kerkhof P, Nieboer C, Austad J et al. Comparative effects of two different calcipotriol (MC 903) cream formulations versus placebo in psoriasis vulgaris. A randomised, double-blind, placebo-controlled, parallel group multi-centre study 1. Journal of the European Academy of Dermatology and Venereology. 1996; 6(2):152-158

7 Langley RG, Gupta A, Papp K, Wexler D, Osterdal ML, Curcic D. Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial. Dermatology. 2011; 222(2):148-156

8 Medansky RS, Brody NI, Kanof NB, Russo GJ, Peets EA. Clinical investigations of mometasone furoate - a novel nonfluorinated, topical corticosteroid. Seminars in Dermatology. 1987; 6(2):94-100

9 Sears HW. A double-blind, randomized, placebo-controlled evaluation of the efficacy and safety of hydrocortisone buteprate 0.1% cream in the treatment of psoriasis. Advances in Therapy. 1997; 14(3):140-149

10 Katz HI, Prawer SE, Medansky RS, Krueger GG, Mooney JJ, Jones ML et al. Intermittent corticosteroid maintenance treatment of psoriasis: a double-blind multicenter trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. Dermatologica. 1991; 183(4):269-274

11 Weinstein GD, Krueger GG, Lowe NJ, Duvic M, Friedman DJ, Jegasothy BV et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. Journal of the American Academy of Dermatology. 1997; 37(1):85-92

12 Weinstein GD. Safety, efficacy and duration of therapeutic effect of tazarotene used in the treatment of plaque psoriasis. British Journal of Dermatology. 1996; 135(Suppl 49):32-36

13 Gottlieb AB, Ford RO, Spellman MC. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. Journal of Cutaneous Medicine and Surgery. 2003; 7(3):185-192

14 Berth-Jones J, Chu AC, Dodd WA, Ganpule M, Griffiths WA, Haydey RP et al. A multicentre, parallel-group comparison of calcipotriol ointment and short-contact dithranol therapy in chronic plaque psoriasis. British Journal of Dermatology. 1992; 127(3):266-271

15 Alora-Palli MB, Perkins AC, Van Cott A, Kimball AB. Efficacy and tolerability of a cosmetically acceptable coal tar solution in the treatment of moderate plaque psoriasis: a controlled comparison with calcipotriene (calcipotriol) cream. American Journal of Clinical Dermatology. 2010; 11(4):275-283

16 Pinheiro N. Comparative effects of calcipotriol ointment (50 micrograms/g) and 5% coal tar/2% allantoin/0.5% hydrocortisone cream in treating plaque psoriasis. British Journal of Clinical Practice. 1997; 51(1):16-19

17 Barker JN, Ashton RE, Marks R, Harris RI, Berth-Jones J. Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose-finding study with active comparator. British Journal of Dermatology. 1999; 141(2):274-278

18 Barker JN, Griffiths CE. Combination therapy for psoriasis. Dermatologic Therapy. 1999; 11:96-103

19 Perez A, Chen TC, Turner A, Raab R, Bhawan J, Poche P et al. Efficacy and safety of topical calcitriol (1,25-dihydroxyvitamin d3) for the treatment of psoriasis. British Journal of Dermatology. 1996; 134(2):238-246

20 Fleming C, Ganslandt C, Guenther L, Johannesson A, Buckley C, Simon JC et al. Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study. European Journal of Dermatology. 2010; 20(4):465-471

21 Kaufmann R, Bibby A, Bissonnette R, Cambazard F, Chu A, Decroix J et al. A new calcipotriol/betamethasone dipropionate formulation (DaivobetTM) is an fffective once-daily treatment for psoriasis vulgaris. Dermatology. 2002; 205(4):389-393

22 Decroix J, Pres H, Tsankov N, Poncet M, Arsonnaud S. Clobetasol propionate lotion in the treatment of moderate to severe plaque-type psoriasis. Cutis. 2004; 74(3):201-206

23 Weinstein GD, Koo JY, Krueger GG, Lebwohl MG, Lowe NJ, Menter MA et al. Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. Journal of the American Academy of Dermatology. 2003; 48(5):760-767

24 Langner A, Verjans H, Stapor V, Mol M, Fraczykowska M. 1alpha, 25-Dihydroxyvitamin D_3 (calcitriol) ointment in psoriasis. Journal of Dermatological Treatment. 1992; 3(4):177-180

25 Langner A, Verjans H, Stapor V, Mol M, Fraczykowska M. Topical calcitriol in the treatment of chronic plaque psoriasis: a double-blind study. British Journal of Dermatology. 1993; 128(5):566-571

26 Papp KA, Guenther L, Boyden B, Larsen FG, Harvima RJ, Guilhou JJ et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. Journal of the American Academy of Dermatology. 2003; 48(1):48-54

27 Guenther L, van de Kerkhof PC, Snellman E, Kragballe K, Chu AC, Tegner E et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. British Journal of Dermatology. 2002; 147(2):316-323

28 Wortzel WH. A new corticosteroid for moderate/severe dermatoses. Clinical Medicine. 1975; 82(3):23-26

29 Lowe N, Feldman SR, Sherer D, Weiss J, Shavin JS, Lin YL et al. Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. Journal of Dermatological Treatment. 2005; 16(3):158-164

30 Gottlieb A, Chaudhari U, Baker D, Perate M, Dooley LT. The National Psoriasis Foundation Psoriasis Score (NPF-PS) system versus the Psoriasis Area Severity Index (PASI) and Physician's Global Assessment (PGA): a comparison. Journal of Drugs in Dermatology: JDD. 2003; 2(3):260-266

31 Lebwohl M, Sherer D, Washenik K, Krueger GG, Menter A, Koo J et al. A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. International Journal of Dermatology. 2002; 41(5):269-274

32 Jarratt MT, Clark SD, Savin RC, Swinyer LJ, Safley CF, Brodell RT et al. Evaluation of the efficacy and safety of clobetasol propionate spray in the treatment of plaque-type psoriasis. Cutis. 2006; 78(5):348-354

33 Kragballe K, Barnes L, Hamberg KJ, Hutchinson P, Murphy F, Moller S et al. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. British Journal of Dermatology. 1998; 139(4):649-654

34 Ortonne P, Kaufmann R, Lecha M, Goodfield M. Efficacy of treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris: a randomised, double-blind trial. Dermatology. 2004; 209(4):308-313

35 Camarasa JM, Ortonne JP, Dubertret L. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. Journal of Dermatological Treatment. 2003; 14(1):8-13

36 Molin L. Does addition of topical calcipotriol to UVB increase the risk of irritant reactions in psoriasis? The Calcipotriol-UVB Study Group. Acta Dermato-Venereologica. 1997; 77(5):401-402

37 Cunliffe WJ, Berth-Jones J, Claudy A, Fairiss G, Goldin D, Gratton D et al. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. Journal of the American Academy of Dermatology. 1992; 26(5 Pt 1):736-743

38 Douglas WS, Poulin Y, Decroix J, Ortonne JP, Mrowietz U, Gulliver W et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Dermato-Venereologica. 2002; 82(2):131-135

39 Ruzicka T, Lorenz B. Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicentre, double-blind, randomized study. British Journal of Dermatology. 1998; 138(2):254-258

40 Tham SN, Lun KC, Cheong WK. A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis. British Journal of Dermatology. 1994; 131(5):673-677

41 Hutchinson P, Marks R, White J. The efficacy, safety and tolerance of calcitriol 3 microg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. Dermatology. 2000; 201(2):139-145

42 Wall AR, Poyner TF, Menday AP. A comparison of treatment with dithranol and calcipotriol on the clinical severity and quality of life in patients with psoriasis. British Journal of Dermatology. 1998; 139(6):1005-1011

43 Christensen OB, Mork N-J, Ashton R, Daniel F, Anehus S. Comparison of a treatment phase and a follow-up phase of short-contact dithranol and calcipotriol in outpatients with chronic plaque psoriasis. Journal of Dermatological Treatment. 1999; 10(4):261-265

44 Menter A, Abramovits W, Colon LE, Johnson LA, Gottschalk RW. Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. Journal of Drugs in Dermatology: JDD. 2009; 8(1):52-57

45 Thawornchaisit P, Harncharoen K. A comparative study of tar and betamethasone valerate in chronic plaque psoriasis: a study in Thailand. Journal of the Medical Association of Thailand. 2007; 90(10):1997-2002

46 Buckley C, Hoffmann V, Shapiro J, Saari S, Cambazard F, Milsgaard M. Calcipotriol plus betamethasone dipropionate scalp formulation is effective and well tolerated in the treatment of scalp psoriasis: a phase II study. Dermatology. 2008; 217(2):107-113

47 Franz TJ, Parsell DA, Halualani RM, Hannigan JF, Kalbach JP, Harkonen WS. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. International Journal of Dermatology. 1999; 38(8):628-632

48 Green C, Ganpule M, Harris D, Kavanagh G, Kennedy C, Mallett R et al. Comparative effects of calcipotriol (MC903) solution and placebo (vehicle of MC903) in the treatment of psoriasis of the scalp. British Journal of Dermatology. 1994; 130(4):483-487

49 Jarratt M, Breneman D, Gottlieb AB, Poulin Y, Liu Y, Foley V. Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. Journal of Drugs in Dermatology: JDD. 2004; 3(4):367-373

50 Jemec GB, Ganslandt C, Ortonne JP, Poulin Y, Burden AD, de Unamuno P et al. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. Journal of the American Academy of Dermatology. 2008; 59(3):455-463

51 Kragballe K, Hoffmann V, Ortonne JP, Tan J, Nordin P, Segaert S. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. British Journal of Dermatology. 2009; 161(1):159-166

52 Olsen EA, Cram DL, Ellis CN, Hickman JG, Jacobson C, Jenkins EE et al. A double-blind, vehicle-controlled study of clobetasol propionate 0.05% (Temovate) scalp application in the treatment of moderate to severe scalp psoriasis. Journal of the American Academy of Dermatology. 1991; 24(3):443-447

53 Reygagne P, Mrowietz U, Decroix J, de Waard-van der Spek FB, Acebes LO, Figueiredo A et al. Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. Journal of Dermatological Treatment. 2005; 16(1):31-36

54 Tyring SK, Mendoza N, Appell M, Bibby A, Foster R, Hamilton T et al. A calcipotriene/betamethasone dipropionate two-compound scalp formulation in the treatment of scalp psoriasis in Hispanic/Latino and Black/African American patients: Results of the randomized, 8-week, double-blind phase of a clinical trial. International Journal of Dermatology. 2010; 49(11):1328-1333

55 van de Kerkhof PC, Hoffmann V, Anstey A, Barnes L, Bolduc C, Reich K et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. British Journal of Dermatology. 2009; 160(1):170-176

56 Franz TJ, Parsell DA, Myers JA, Hannigan JF. Clobetasol propionate foam 0.05%: a novel vehicle with enhanced delivery. International Journal of Dermatology. 2000; 39(7):535-538

57 Klaber MR, Hutchinson PE, Pedvis-Leftick A, Kragballe K, Reunala TL, van de Kerkhof PC et al. Comparative effects of calcipotriol solution (50 micrograms/ml) and betamethasone 17-valerate solution (1 mg/ml) in the treatment of scalp psoriasis. British Journal of Dermatology. 1994; 131(5):678-683

58 McKinnon C, Klaber MR. Calcipotriol (Dovonex) scalp solution in the treatment of scalp psoriasis: comparative efficacy with 1% coal tar/1% coconut oil/0.5% salicylic acid (Capasal) shampoo, and long-term experience. Journal of Dermatological Treatment. 2000; 11(1):21-28

59 Sofen H, Hudson CP, Cook-Bolden FE, Preston N, Colon LE, Caveney SW et al. Clobetasol propionate 0.05% spray for the management of moderate-to-severe plaque psoriasis of the scalp: Results from a randomized controlled trial. Journal of Drugs in Dermatology: JDD. 2011; 10(8):885-892

60 Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CE. Cost-effectiveness analysis of topical calcipotriol versus short-contact dithranol: In the treatment of mild to moderate plaque psoriasis. Pharmacoeconomics. 2000; 18(5):469-476

61 Oh PI, Gupta AK, Einarson TR, Maerov P, Shear NH. Calcipotriol in the treatment of psoriasis of linited sverity: pharacoeconomic evaluation. Journal of Cutaneous Medicine and Surgery. 1997; 2(1):7-15

62 Bottomley JM, Auland ME, Morais J, Boyd G, Douglas WS. Cost-effectiveness of the two-compound formulation calcipotriol and betamethasone dipropionate compared with commonly used topical treatments in the management of moderately severe plaque psoriasis in Scotland. Current Medical Research and Opinion. 2007; 2(8):1887-1901

63 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2009. Available from:

http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp

64 Schofield, J, Grindlay, D, and Williams, H. Skin conditions in the UK: a health needs assessment. Nottingham: Centre of Evidence Based Dermatology, University of Nottingham, 2009

65 Dawe RS, Wainwright NJ, Cameron H, Ferguson J. Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment? British Journal of Dermatology. 1998; 138(5):833-839

66 Hallaji Z, Barzegari M, Balighi K, Taheri A, Mansoori P. A comparison of three times vs. five times weekly narrowband ultraviolet B phototherapy for the treatment of chronic plaque psoriasis. Photodermatology, Photoimmunology and Photomedicine. 2010; 26(1):10-15

67 Cameron H, Dawe RS, Yule S, Murphy J, Ibbotson SH, Ferguson J. A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. British Journal of Dermatology. 2002; 147(5):973-978

68 van de Kerkhof PC, Van Der Valk PG, Swinkels OQ, Kucharekova M, de Rie MA, de Vries HJ et al. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day-care setting. British Journal of Dermatology. 2006; 155(4):800-807

69 Curtis L. Unit costs of social health care. Canterbury: Personal Social Services Reseach Unit, University of Kent; 2010. Available from: http://www.pssru.ac.uk/pdf/uc/uc2010/uc2010.pdf

70 Department of Health. NHS reference costs 2009-2010. 2011. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459 [Last accessed: 1 August 2011]

71 Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. Br J Dermatol. 1996; 135(4):533-537

72 Joint Formulary Committee. British national formulary (BNF). 62nd edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2011. Available from: http://www.bnf.org.uk

73 Fleming C, Ganslandt C, Leese GP. Short- and long-term safety assessment of a two-compound ointment containing calcipotriene/betamethasone dipropionate (Taclonex/Daivobet/Dovobet ointment): hypothalamic-pituitary-adrenal axis function in patients with psoriasis vulgaris. Journal of Drugs in Dermatology: JDD. 2010; 9(8):969-974

74 Richards HL, Fortune DG, Griffiths CE. Adherence to treatment in patients with psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV. 2006; 20(4):370-379

75 Lloyd A, Swinburn P, Edson E, Bowman L, Boye KS, Janssen B et al. Development of the EQ-5D-Psoriasis. 27th Scientific Plenary Meeting of the EuroQol Group - Proceedings. 2010;(229):242

76 Affleck AG, Bottomley JM, Auland ME, Jackson P, Ryttov J. Cost effectiveness of the two-compound formulation calcipotriol and betamethasone dipropionate gel in the treatment of scalp psoriasis in Scotland. Current Medical Research and Opinion. 2011; 27(1):269-284

77 Jemec GB, van de Kerkhof PC, Enevold A, Ganslandt C. Significant one week efficacy of a calcipotriol plus betamethasone dipropionate scalp formulation. Journal of the European Academy of Dermatology and Venereology. 2011; 25(1):27-32

78 Bottomley JM, Taylor RS, Ryttov J. The effectiveness of two-compound formulation calcipotriol and betamethasone dipropionate gel in the treatment of moderately severe scalp psoriasis: A systematic review of direct and indirect evidence. Current Medical Research and Opinion. 2011; 27(1):251-268

79 National Institute for Health and Clinical Excellence. Etanercept and efalizumab for the treatment of adults with psoriasis. NICE technology appraisal 103. London: National Institute for Health and Clinical Excellence, 2006 Available from: http://guidance.nice.org.uk/TA103

80 National Institute for Health and Clinical Excellence. Infliximab for the treatment of adults with psoriasis. NICE technology appraisal 134. London: National Institute for Health and Clinical Excellence, 2008 Available from: http://www.nice.org.uk/TA134

81 National Institute for Health and Clinical Excellence. Adalimumab for the treatment of adults with psoriasis. NICE technology appraisal 146. London: National Institute for Health and Clinical Excellence, 2008 Available from: http://guidance.nice.org.uk/TA146

82 National Institute for Health and Clinical Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis. NICE technology appraisal 180. London: National Institute for Health and Clinical Excellence, 2009 Available from: http://guidance.nice.org.uk/TA180

83 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence; 2008. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

84 Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technology Assessment. 2006; 10(46):1-252

85 Joint Formulary Committee. British national formulary (BNF). 59th edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2010. Available from: http://bnf.org/bnf/bnf/current/index.htm

86 Chalmers R, Kirby B, Smith A, Burrows P, Little R, Horan M et al. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. British Journal of Dermatology. 2005; 152(3):444-450

87 Driessen RJ, Bisschops LA, Adang EM, Evers AW, van de Kerkhof PC, de Jong EM. The economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics. British Journal of Dermatology. Netherlands 2010; 162(6):1324-1329

88 Woods AL, Rutter KJ, Gardner LS, Lewis VJ, Saxena S, George SA et al. Inpatient management of psoriasis: a multicentre service review to establish national admission standards. British Journal of Dermatology. 2008; 158(2):266-272

89 Fonia A, Jackson K, Lereun C, Grant DM, Barker JNWN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. British Journal of Dermatology. 2010; 163(4):807-816

90 Department of Health. NHS reference costs 2003 and national tariff 2004 ('payment by results core tools 2004'). 2004. Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4070195&chk=UzhHA3 [Last accessed: 23 November 2004]

91 Department of Health. Hospital episode statistics England: financial year 2002-03. 2003. Available from: http://www.dh.gov.uk/assetRoot/04/06/74/03/04067403.pdf [Last accessed: 12 December 2004]

92 Laws PM, Downs AM, Parslew R, Dever B, Smith CH, Barker JN et al. Practical experience of Ustekinumab in the treatment of psoriasis: experience from a multicentre, retrospective case cohort study across the U.K. and Ireland. British Journal of Dermatology. 2012; 166(1):189-195

93 Papp K, Ho V, Teixeira HD, Guerette K, Chen K, Lynde C. Efficacy and safety of adalimumab when added to inadequate therapy for the treatment of psoriasis: results of PRIDE, an open-label, multicentre, phase IIIb study [submitted]. Journal of the European Academy of Dermatology and Venereology. 2011; Epub

94 Griffiths CE, Strober BE, van de Kerkhof PC, Ho V, Fidelus-Gort R, Yeilding N et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. New England Journal of Medicine. 2010; 362(2):118-128