British Association of Dermatologists guideline for the management of people with vitiligo 2021

Supplementary information

Contents

List of tables

Abbreviations

5-FU	5- flurouracil
8-MOP	8-methoxypsoralen
BAD	British Association of Dermatologists
bFNE	Brief fear of negative evaluation scale
BG	Blister roof grafting
BMI	Body mass index
BSA	Body surface area
CBC	Complete Blood Count
CBSH	Cognitive Behavioural Self-Help
CBT	Cognitive Behavioural Therapy
CDLQI	Children's dermatology life quality index
CHM	Chinese Herbal Medicine
CHU9D	Child Health Utility
CI	Confidence interval
CMT	Cultured melanocyte transplant
CO_2	Carbon dioxide
DAS-24	Derriford Appearance Scale
DHA	Dihydroxyacetone
DLQI	Dermatology life quality index
ECS	Epidermal cell suspension
EG	Epidermal graft
EL	Excimer laser
EMT	Epidermal Melanocyte Transfer
EQ-5D	EuroQoL – 5 dimensions
F	Female
FCS	Follicular Cell Suspension
FP	Fluticosone propionate
FRR	Future Research Recommendation
GAD-2	Generalised Anxiety Disorder Scale
GDG	Guideline development group
GP	General Practitioner
GPwER	General practitioner with extended roles
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
H_2O_2	Hydrogen peroxide
HADS	Hospital Anxiety and Depression Scale
HFMT	Hair Follicular Melanocyte Transfer
HH-HBP	Hand-Held Home-Based Phototherapy
IBEL	Institution Based Excimer Lamp
IQR	Interquartile range
ITT	Intention to treat
LETR	Linking evidence to ecommendation
LT	Latanoprost
M	Male
MBEH	Monobenzyl ether of hydroquinone
MD	Mean difference
MEL	Monochromatic Excimer Light
MID	Minimally important difference
MKT	Melanocytes-keratinocytes transplantation

Mo.	Month
MPD	Oralmethylprednisolone
MPG	Miniature punch grafting
MTX	Methotrexate
NA	Not applicable
NB-UVB	Narrowband ultraviolet B
NCES	Nocturnal epidermal cell suspension
Nd: YAG	Neodymium-doped yttrium aluminium garnet
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NR	Not reported
NSV	Non-segmental vitiligo
OCG	Oral compound glycyrrhizin
OD	Once daily
OMP	Oral minipulses
PC-KUS	Pseudocatalase
PCT	Person centred therapy
PGA	Physician global assessment
PHQ-4	The 4-item health questionnaire
PHQ-9	The 9-item health questionnaire
PICO	Patient intervention comparison outcome
PRP	Platelet rich plasma
PUVA	Psoralens ultraviolet A
QoL	Quality of life
QSR	Q-switched ruby
RR	Risk ratio
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SEM	Standard error of mean
SPF	Sun protection factor
SPT	Skin phototype
TMP	Trimethylpsoralen
UK	United Kingdom
USA	United states of America
UTSG	Ultra-thin skin grafting
UV	Ultraviolet
UVB	Ultraviolet B
VAS	Visual analogue scale
VASI	Vitiligo Area Scoring Index
VCD	Voluntary Cosmetic Depigmentation
VETF	Vitiligo European Task Force
VIDA	Vitiligo disease activity
VIPs	Vitiligo impact patient scale
VitiQoL	Vitiligo Specific health related Quality of Life
VNS	Vitiligo noticeability scale
Wk.	Week
Yr.	Year

Appendix A: Review protocol

Question 1

Topical treatments in people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness and safety of topical therapies compared with each other, with placebo or combination of topical plus other active therapies?
Objectives	The aim of this review is to assess the clinical effectiveness and safety of topical therapies for the management of patients with vitiligo to each other, to placebo or combination of topical plus other active therapies for the management of patients with vitiligo
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Active vs. old lesions • Skin type

Intervention	• Topical treatments
	  ○ Corticosteroids
	  ○ Vitamin D analogues
	  ○ Calcineurin inhibitors
	  ○ Other topical treatments e.g. Pseudocatalase, antioxidant preparations

Comparison	• Placebo • Topical corticosteroids • Other active treatment
Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • Quality of Life (QoL) (7) ***Important*** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: Studies with fewer than 10 participants will not be considered
Setting	• Secondary care

	• Tertiary care
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 2

Depigmentation treatments in people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness and safety of depigmentation treatment compared with other active treatments or placebo?
Objectives	The aim of this review is to assess the clinical effectiveness and safety of depigmentation treatment compared to other active treatments or placebo for the management of patients with vitiligo
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Skin type
Intervention	• Topical hydroquinone derivatives • Laser
Comparison	• No treatment • Other active treatment to achieve depigmentation
Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Degree of depigmentation (9) • Patient rating of appearance (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) ***Important*** • Risk of re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: No minimum
Setting	• Secondary care • Tertiary care
Search Strategy	Appendix L
Review strategy	Appraisal of methodological quality

	• The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 3

Systemic treatments in people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness and safety of systemic therapies compared with placebo, other active therapies, or combination of systemic plus other active therapies?
Objectives	The aim of this review is to assess the clinical effectiveness and safety of systemic therapies for the management of patients with vitiligo with placebo, other active therapies, or combination of systemic plus other active therapies.
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Active vs. Old lesions • Skin type
Intervention	• Systemic treatments (to be specified once we identify treatments during data extraction)
Comparison	• Placebo • Topical corticosteroids • Other active therapies • Combination of systemic plus other active therapies
Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) ***Important*** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: no minimum
Setting	• Secondary care

	• Tertiary care
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 4

Light treatments for people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness of a course of light therapy [narrowband Ultraviolet B (NB-UVB), psoralens ultraviolet A (PUVA), PUVA-sol)] compared with each other, other active therapies, placebo or combination of light therapy plus other active therapies?
Objectives	The aim of this review is to assess the clinical effectiveness of a course of light therapy (NB-UVB, PUVA, PUVA-sol) for the management of patients with vitiligo with each other, other active therapies, placebo or combination of light therapy plus other active therapies.
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Active vs. stable lesions • Skin type

Intervention	• Light therapies
	  ○ NB-UVB
	  ○ PUVA
	  ○ PUVA-sol

Comparison	• Placebo
	• Light therapies
	  ○ NB-UVB
	  ○ PUVA
	  ○ PUVA-sol
	  ○ Excimer light
	  ○ Laser
	• Other active treatment

Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) ***Important***

	• Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: Studies with fewer than 10 participants will not be considered
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 5

Laser treatments in people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness of a course of laser or excimer light therapy compared with each other, other active therapies, placebo or combination of laser or excimer light therapy plus other active therapies?
Objectives	The aim of this review is to assess the clinical effectiveness of a course of laser or excimer light therapy for the management of patients with vitiligo with each other, other active therapies, placebo or combination of laser or excimer light therapy plus other active therapies.
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (12-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Active vs. stable lesions • Skin type
Intervention	• Excimer light • Laser

Comparison	• Placebo
	• Light therapies
	  ○ NB-UVB
	  ○ PUVA
	  ○ PUVA-sol
	  ○ Excimer light
	  ○ Laser
	• Other active treatment

Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) ***Important*** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: No minimum
Setting	• Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 6

Late complications of PUVA or NB-UVB therapy in people with vitiligo

Component	Description
Review question	In people with vitiligo, who have received large doses of PUVA (more than 150 treatment sessions) or NB-UVB (more than 150 treatment sessions) what is the risk of developing premalignant or malignant skin changes compared with people who have not received light therapies and which individuals are at particular risk?
Objectives	The aim of this review is to determine the risk of developing premalignant or malignant skin changes in people who have received large doses of PUVA (more than 150 treatment sessions) or NB-UVB (more than 300 treatment sessions) compared to an unexposed cohort and to establish whether there are particular subgroups of the population at higher risk.
Population	People with vitiligo who have received large doses of PUVA (more than 150 treatment sessions) or NB-UVB (more than 300 treatment sessions)
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Previous skin cancer
Sub-groups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Skin type

Prognostic factors (present/ absence of)	• PUVA (more than 150 treatment sessions) • NB-UVB (more than 300 treatment sessions)
Outcomes	***Critical*** • Melanoma • Squamous Cell Carcinoma (SCC) ***Important*** • Basal Cell Carcinoma • Other skin cancers • Intraepidermal carcinoma (Bowen's disease/SCC *in situ*) ***Less important*** • Actinic keratoses
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: No minimum
Setting	• Secondary care • Tertiary care
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 7

Combination therapy for people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness and safety of one combination therapy compared to another combination
Objectives	The aim of this review is to assess the clinical effectiveness and safety of one combination therapy compared to another combination therapy
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Skin type • Active vs. non-active lesions
Intervention	• Combination therapy
Comparison	• Combination therapy
Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9)

	• Harms of treatment (8) • QoL (7) ***Important*** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size: No minimum
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 8

Surgical interventions for people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness and safety of surgical therapies compared with placebo or other treatments?
Objectives	The aim of this review is to assess the clinical effectiveness and safety of surgical therapies for the management of patients with vitiligo compared to placebo or other treatments.
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Skin type

Intervention	• Surgical therapies
	  ○ Non-cultured autologous cell transplantation
	  ○ Cultured autologous cell transplantation
	  ○ Split thickness skin grafting
	  ○ Blister grafting
	  ○ Dermabrasion with/without laser

Comparison	• Placebo • Other treatments
Outcomes	***Critical***

	• Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) ***Important*** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size No minimum
Setting	• Secondary care • Tertiary care
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 9

Psychological therapy for the treatment of vitiligo

Component	Description
Review question	In people with vitiligo, what psychological interventions are available and what is the effectiveness of these psychological interventions compared with other treatments?
Objectives	The aim of this review is to assess the availability and effectiveness of psychological interventions for the management of patients with vitiligo compared with other treatments?
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Facial vs. non-facial
Intervention	• Any interventions
Comparison	• Any other treatments
Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7)

	Important • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size no minimum
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 10

Skin camouflage for people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness of skin camouflage compared with placebo, other interventions or combination of skin camouflage plus other active therapies?
Objectives	The aim of this review is to assess the clinical effectiveness of skin camouflage for the management of patients with vitiligo compared with placebo other interventions or combination of skin camouflage plus other active therapies.
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Skin type
Intervention	• Skin camouflage, Skin stains, tattoo, other
Comparison	• Placebo • Other interventions
Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7)

	Important • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size no minimum
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Question 11

Complementary therapies for people with vitiligo

Component	Description
Review question	In people with vitiligo, what is the clinical effectiveness complementary therapies compared with placebo, other interventions or combination of complementary therapies plus other active therapies?
Objectives	The aim of this review is to assess the clinical effectiveness of complementary therapies for the management of patients with vitiligo compared with placebo other interventions or combination of complementary therapies plus other active therapies.
Population	All people with vitiligo
Strata	The following groups/interventions will be considered separately if data is available: • Children (up to 12 years) & young people (13-17 years) • Segmental vs. non-segmental • Facial vs. non-facial
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Skin type • Active vs. non-Active lesions
Intervention	• Complementary therapies
Comparison	• Placebo • Other treatments

Outcomes	***Critical*** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) ***Important*** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
Study design	• RCTs or systematic reviews • Cohort studies for long-term efficacy/ safety data • Case control studies/case series
Population size and directness	• Sample size no minimum
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See Appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome.

Appendix B: Forest plots

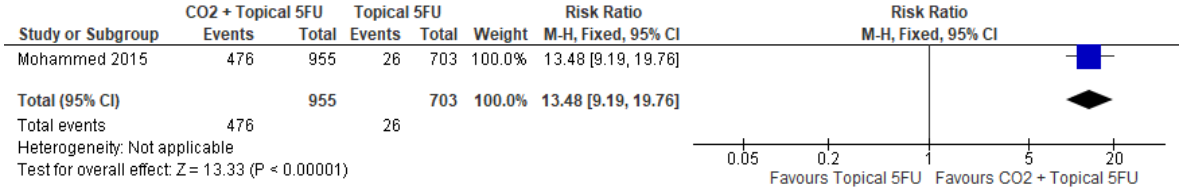
NB: If the outcome being measured is positive, e.g. repigmentation, the intervention will appear on the right-hand axis of the forest plots. If negative, e.g. adverse events, the intervention will appear on the left-hand axis of the forest plots.

Topical Therapies

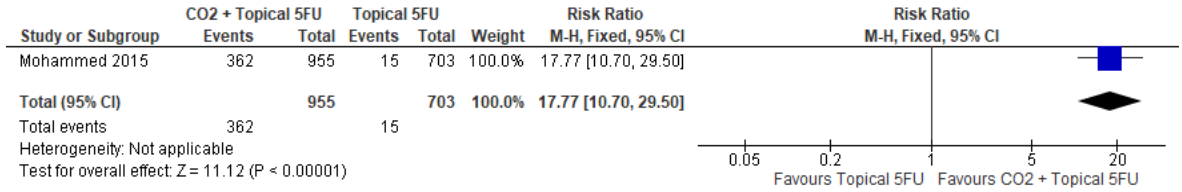
Topical 5-flurouracil (5-FU) + CO_2 laser vs. topical 5-FU

Critical outcomes

- Repigmentation ≥75% in **lesions** on **hands and feet** at 6-month follow-up

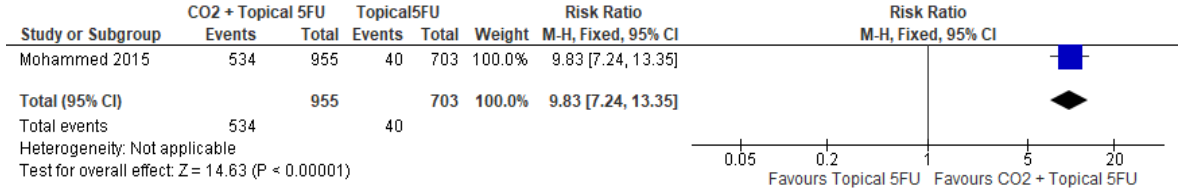


N.B. Complete repigmentation (100%) in lesions on **hands and feet** at 6-month follow-up



Important outcomes

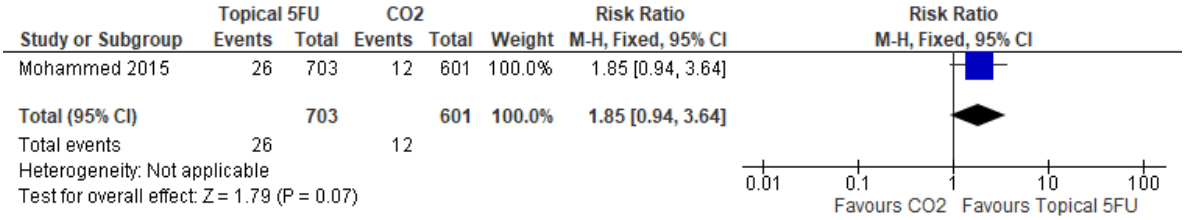
- Repigmentation ≥ 50% in **lesions** on **hands and feet** at 6-month follow-up



Topical 5-FU vs. CO_2 laser

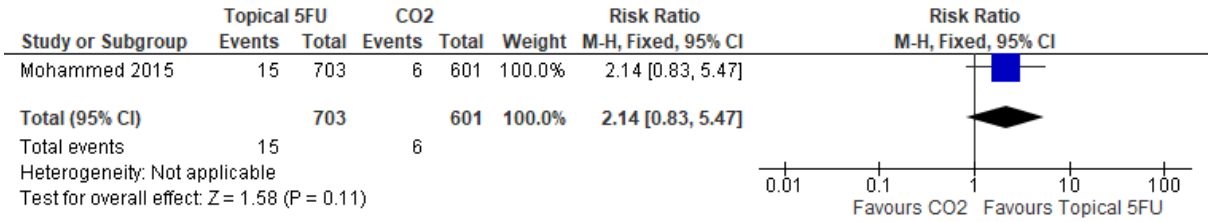
Critical outcomes

- Repigmentation ≥75% in **lesions** on **hands and feet** at 6-month follow-up



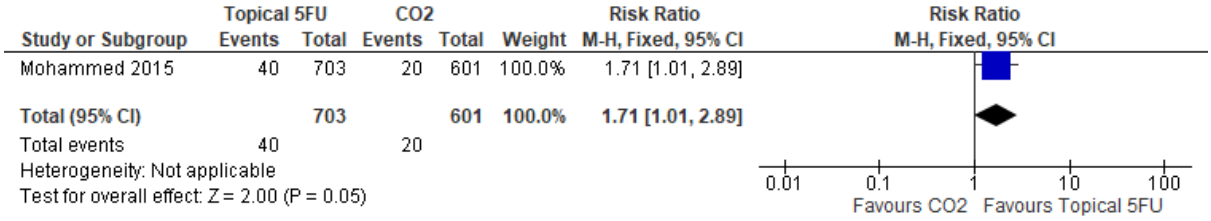
N.B. Change in scale

- Complete repigmentation (100%) in **lesions** on **hands and feet** at 6-month follow-up



Important outcomes

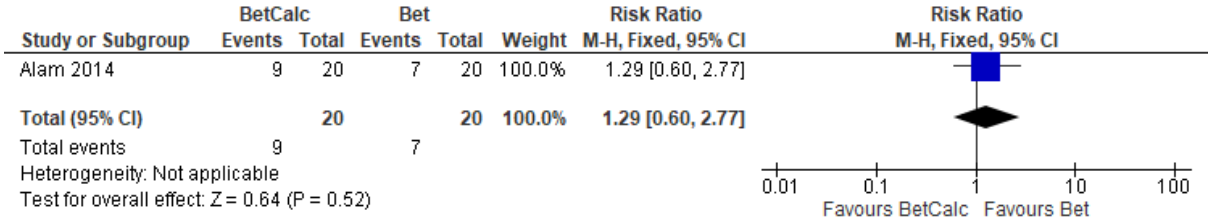
- Repigmentation ≥ 50% in **lesions** on **hands and feet** at 6-month follow-up



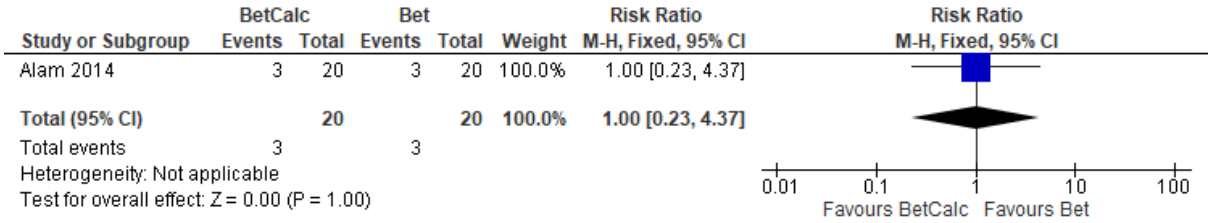
Betamethasone dipropionate (0.05%) cream + calcipotriene (0.005%) ointment vs. betamethasone dipropionate (0.05%) cream

Critical outcomes

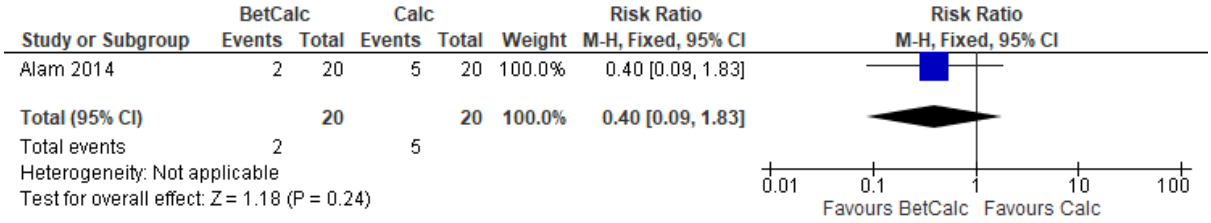
- Erythema in **patients** at 1-month follow-up



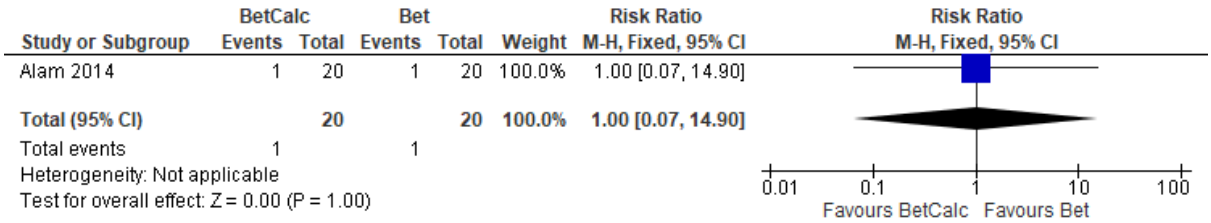
- Erythema in **patients** at 5-month follow-up



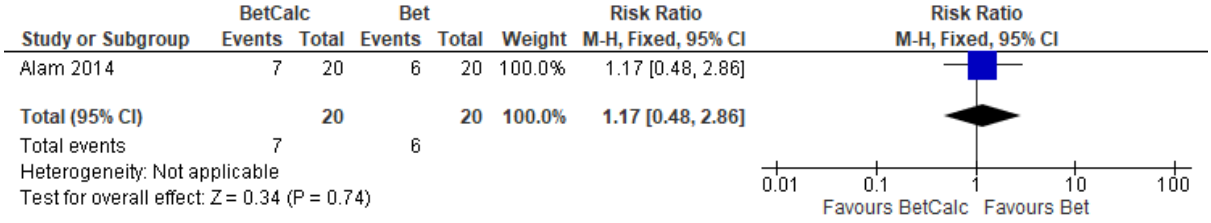
- Scaling in **patients** at 1-month follow-up



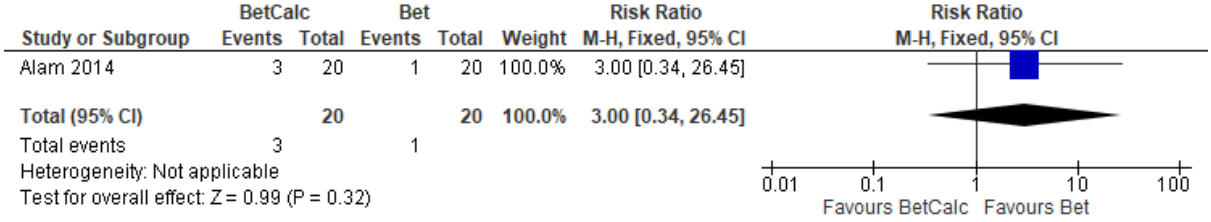
- Scaling in **patients** at 5-month follow-up



- Dryness in **patients** at 1-month follow-up

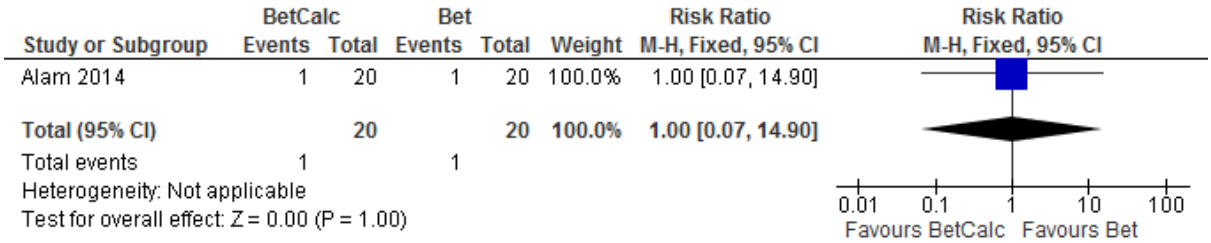


- Dryness in **patients** at 5-month follow-up



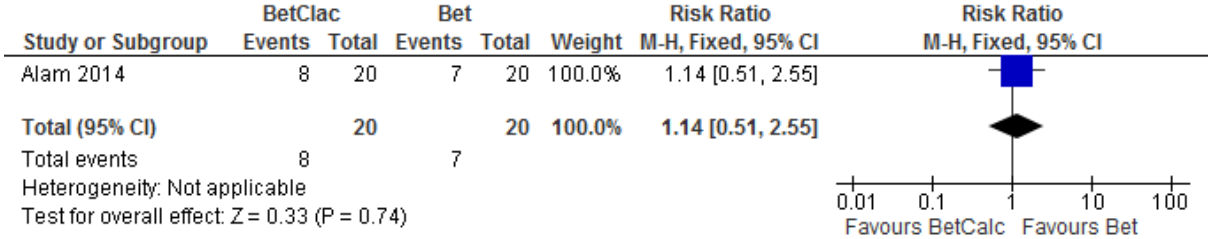
- Pruritus in **patients** at 1-month follow-up

- Pruritus in **patients** at 5-month follow-up



N.B. Change in scale

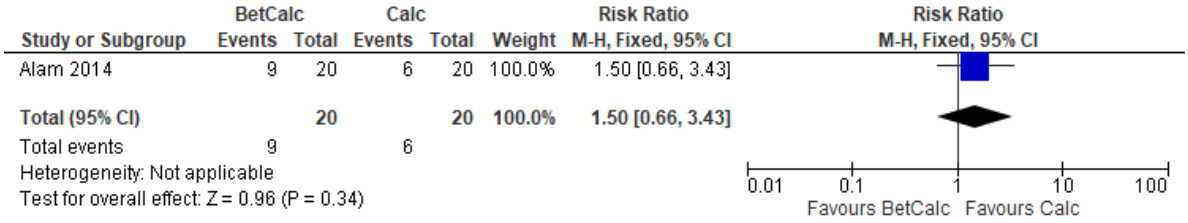
- Burning in **patients** at 1-month follow-up



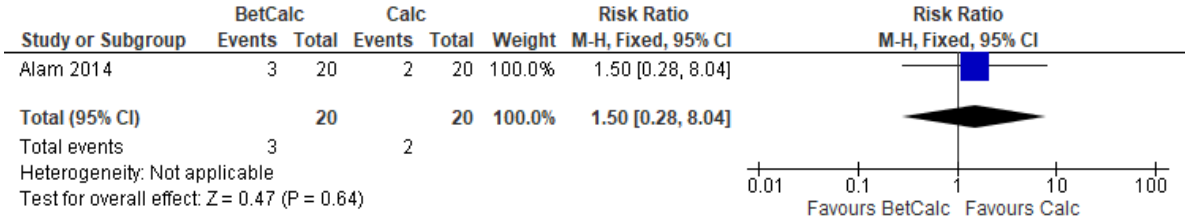
Betamethasone dripropionate (0.05%) cream + calcipotriene (0.005%) ointment vs. calcipotriene (0.005%) ointment

Critical outcomes

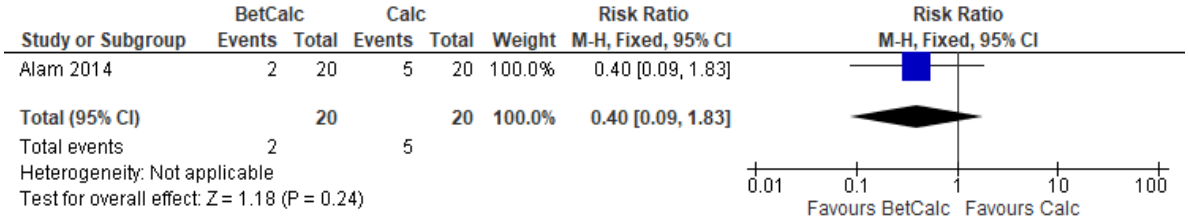
- Erythema in **patients** at 1-month follow-up



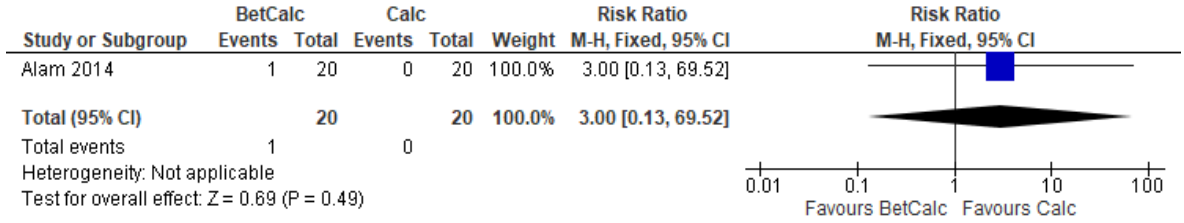
- Erythema in **patients** at 5-month follow-up



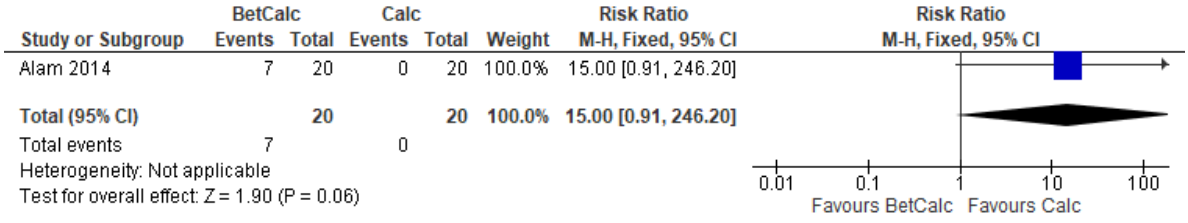
- Scaling in **patients** at 1-month follow-up



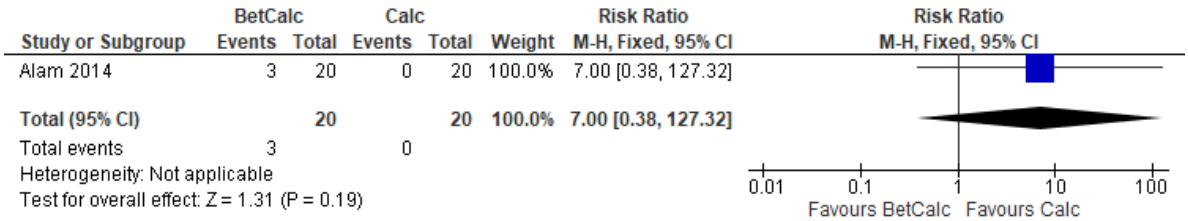
- Scaling in **patients** at 5-months follow-up



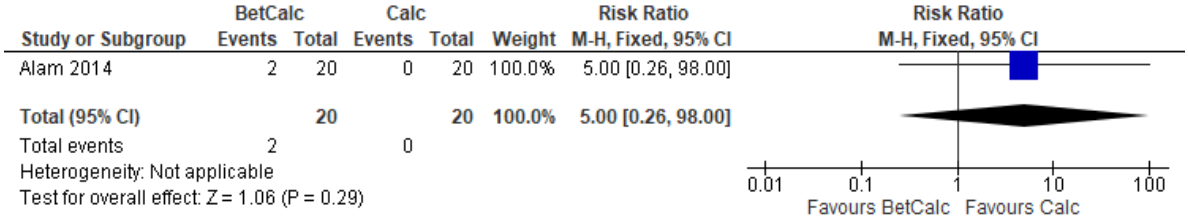
- Dryness in **patients** at 1-month follow-up



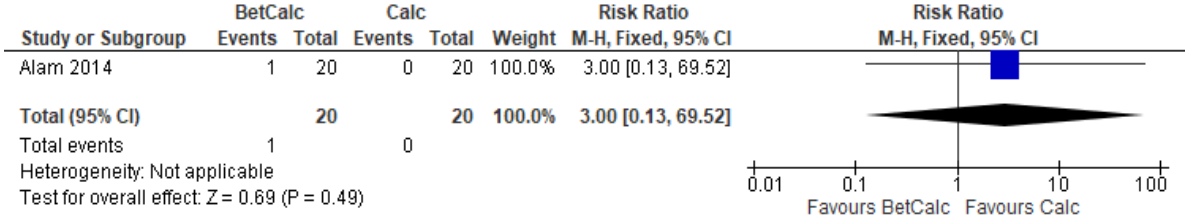
- Dryness in **patients** at 5-month follow-up



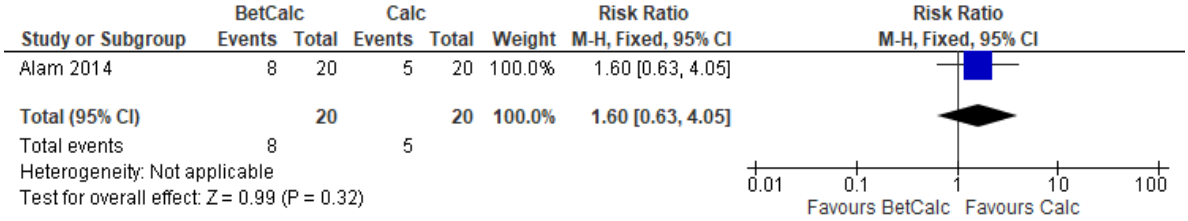
- Pruritus in **patients** at 1-month follow-up



- Pruritus in **patients** at 5-month follow-up



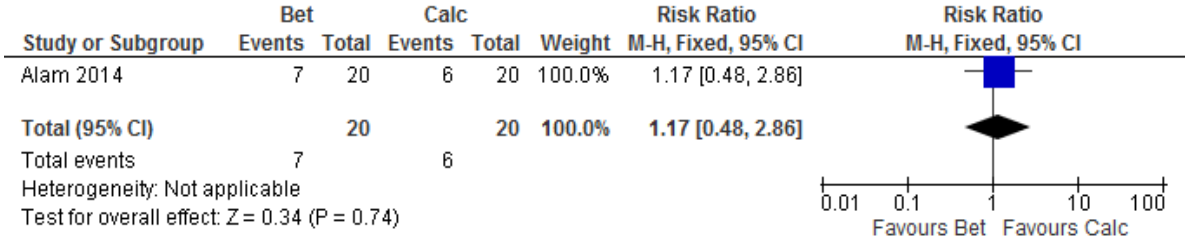
- Burning in **patients** at 1-month follow-up



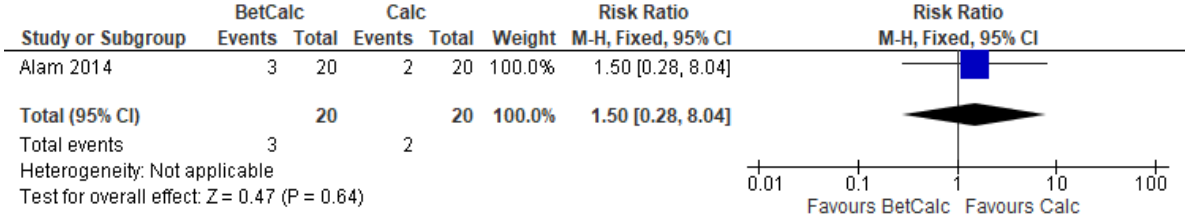
Betamethasone (0.05%) cream vs. calcipotriene (0.005%) ointment

<u>Critical outcomes</u>

- Erythema in **patients** at 1-month follow-up



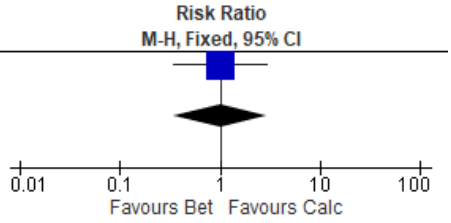
- Erythema in **patients** at 5-month follow-up



- Scaling in **patients** at 1-month follow-up

Study or Subgroup	Bet Events	Bet Total	Calc Events	Calc Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 2014	5	20	5	20	100.0%	1.00 [0.34, 2.93]
Total (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.34, 2.93]**
Total events	5		5			

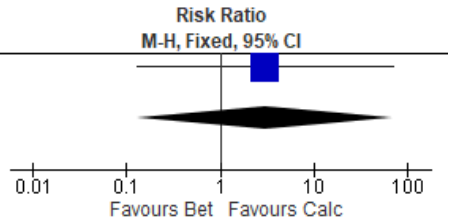
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



- Scaling in **patients** at 5-month follow-up

Study or Subgroup	Bet Events	Bet Total	Calc Events	Calc Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 2014	1	20	0	20	100.0%	3.00 [0.13, 69.52]
Total (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13, 69.52]**
Total events	1		0			

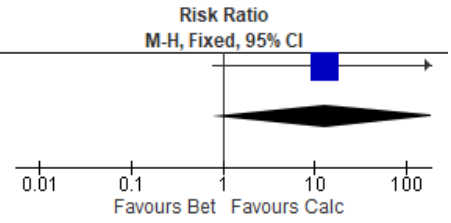
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



- Dryness in **patients** at 1-month follow-up

Study or Subgroup	Bet Events	Bet Total	Calc Events	Calc Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 2014	6	20	0	20	100.0%	13.00 [0.78, 216.39]
Total (95% CI)		**20**		**20**	**100.0%**	**13.00 [0.78, 216.39]**
Total events	6		0			

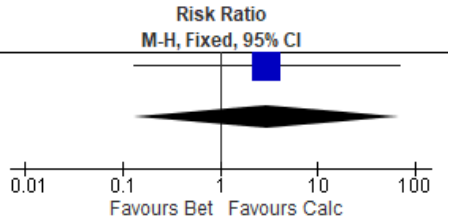
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



- Dryness in **patients** at 5-month follow-up

Study or Subgroup	Bet Events	Bet Total	Calc Events	Calc Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 2014	1	20	0	20	100.0%	3.00 [0.13, 69.52]
Total (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13, 69.52]**
Total events	1		0			

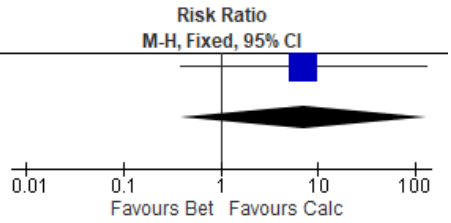
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



- Pruritus in **patients** at 1-month follow-up

Study or Subgroup	Bet Events	Bet Total	Clac Events	Clac Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 2014	3	20	0	20	100.0%	7.00 [0.38, 127.32]
Total (95% CI)		**20**		**20**	**100.0%**	**7.00 [0.38, 127.32]**
Total events	3		0			

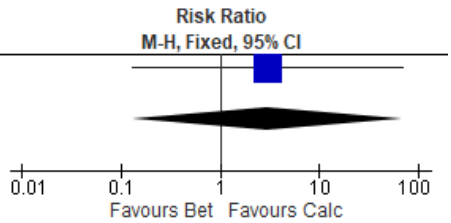
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)



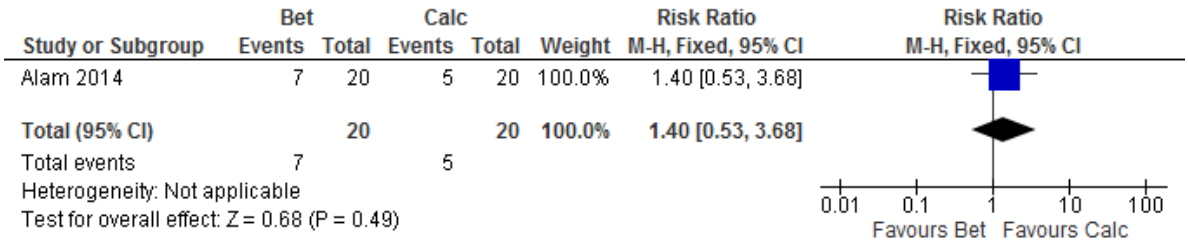
- Pruritus in **patients** at 5-month follow-up

Study or Subgroup	Bet Events	Bet Total	Calc Events	Calc Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alam 2014	1	20	0	20	100.0%	3.00 [0.13, 69.52]
Total (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13, 69.52]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



- Burning in **patients** at 1-month follow-up



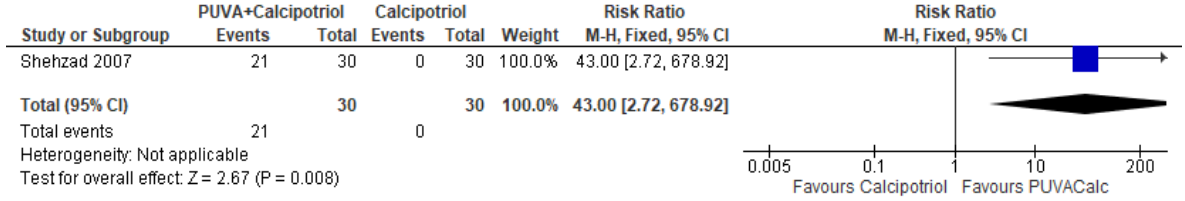
- Burning in **patients** at 5-month follow-up

Burning at 5-month follow-up was zero for both groups so there is no forest plot for this outcome.

PUVA + calcipotriol vs. calcipotriol

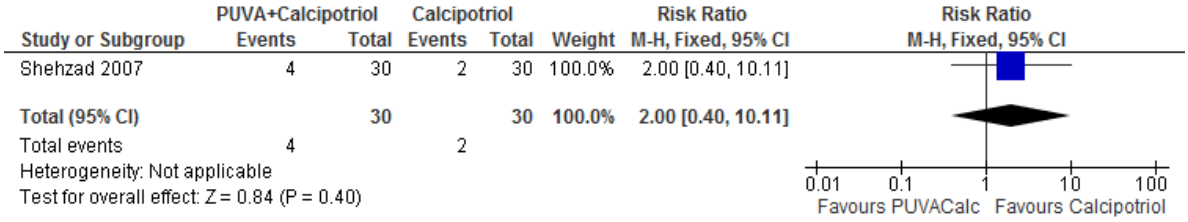
Critical outcomes

- Repigmentation ≥75% (76-100%) in **patients** at 6-month follow-up



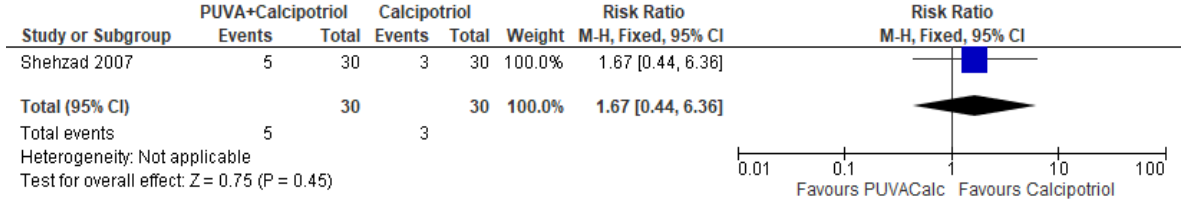
N.B. Change in scale

- Erythema in **patients** at 6-month follow-up

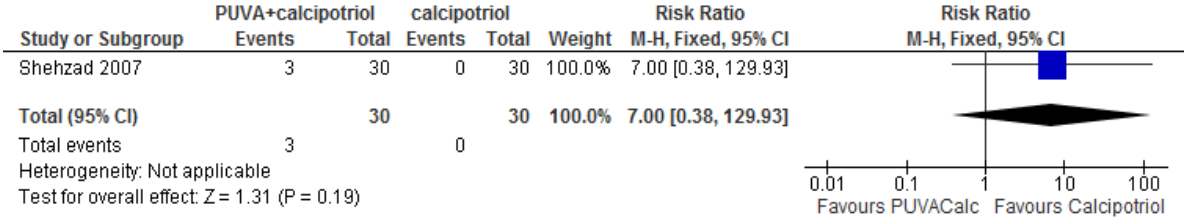


N.B. Change in scale

- Pruritus and burning in **patients** at 6-month follow-up



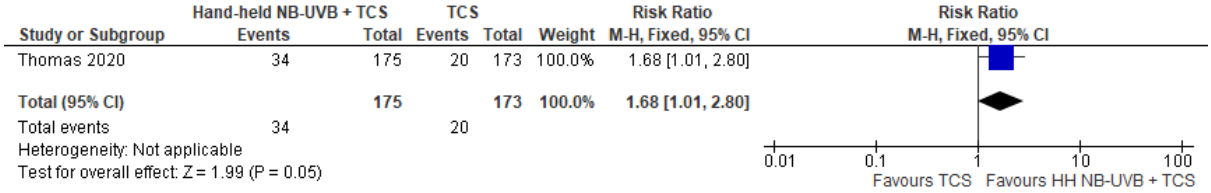
- Nausea and vomiting in **patients** at 6-month follow-up



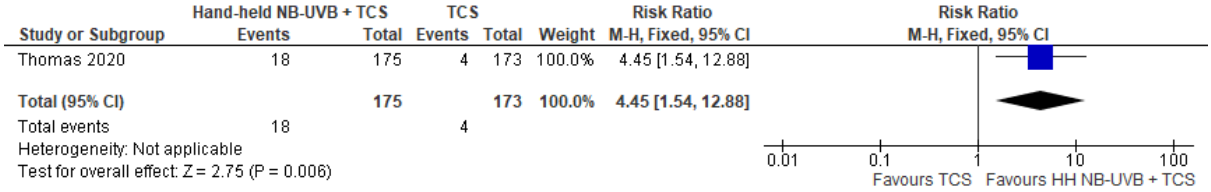
Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)

Critical outcomes

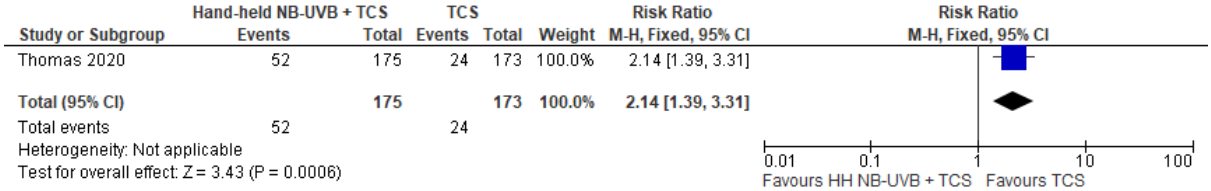
- Patient reported treatment success (a lot less noticeable or no longer noticeable) on Vitiligo noticeability scale (VNS) scale at 9-month follow-up



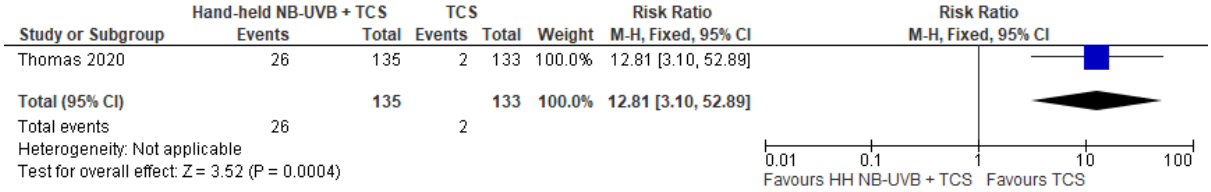
- Repigmentation ≥75% in **patients** at 9-month follow-up



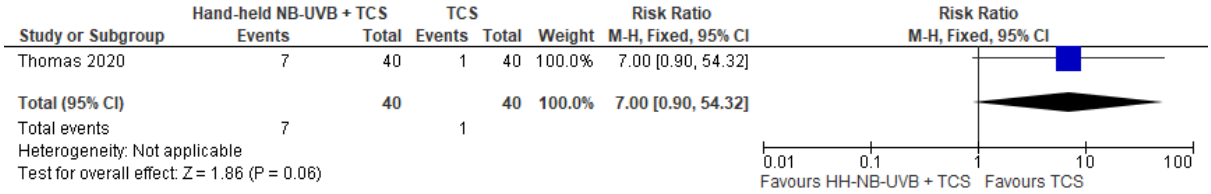
- Treatment-related adverse events in **patients**



- Erythema (Grade 3 and 4) at 9-month follow-up in **adults**

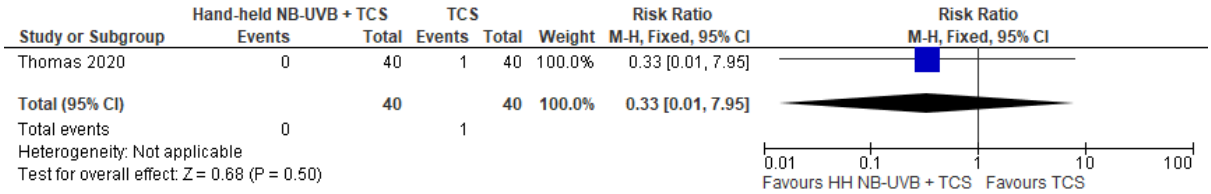


- Erythema (Grade 3 and 4) at 9-month follow-up in **children**

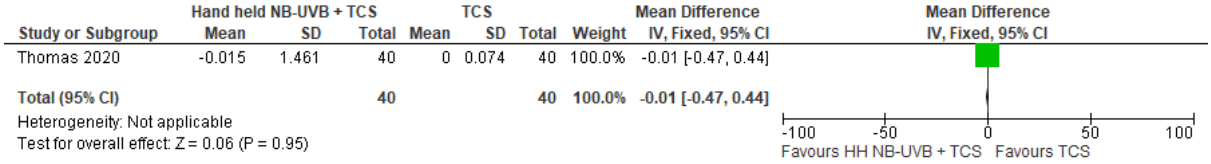


- Skin thinning at 9-month follow-up in **adults**

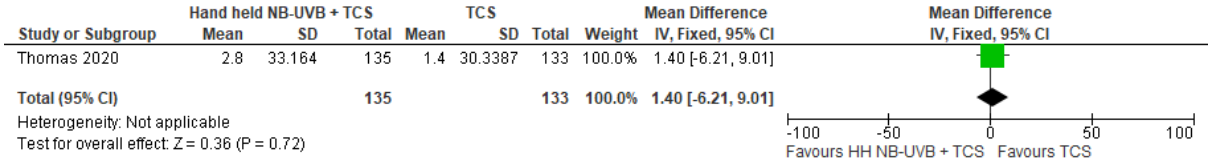
- Skin thinning at 9-month follow-up in **children**



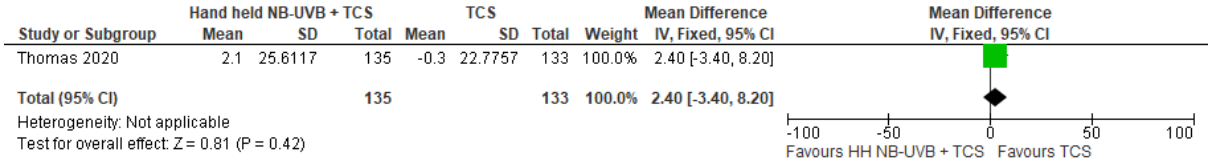
- Change in Child Health Utility (CHU9D) instrument at 9-month follow-up in **children**



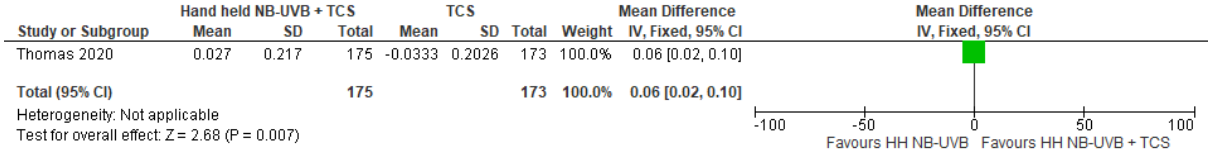
- Change in vitiligo specific health related quality of life (VitiQoL) VitiQoL at 21-month follow-up in **adults**



- Change in Skindex 29 at 21-month follow-up in **adults**



- Change in EuroQoL – 5 dimension (EQ-5D) questionnaire in **patients** at 9-month follow-up



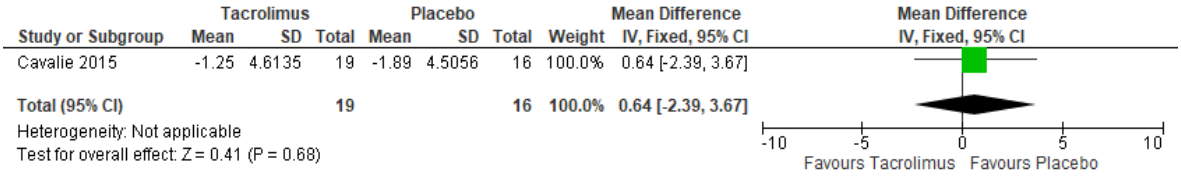
Important outcomes

- Participant reported loss of treatment response at 21-month follow-up in **patients** with treatment success at 9-month follow-up

Tacrolimus 0.1% ointment vs. placebo (unclear what the placebo group was)

Critical outcomes

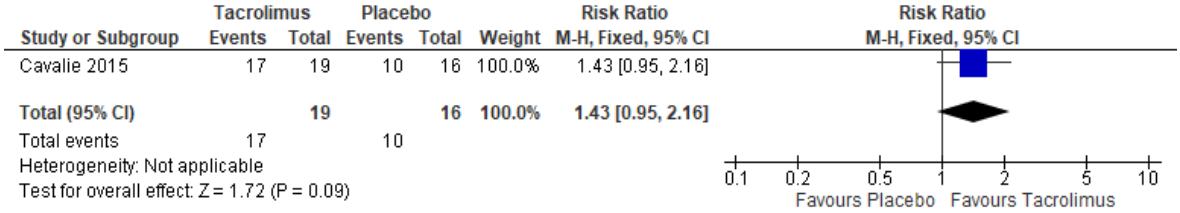
- Improvement in QoL of **patients** at 6-month follow-up using the dermatology life quality index (DLQI)



N.B. Change in scale

Important outcomes

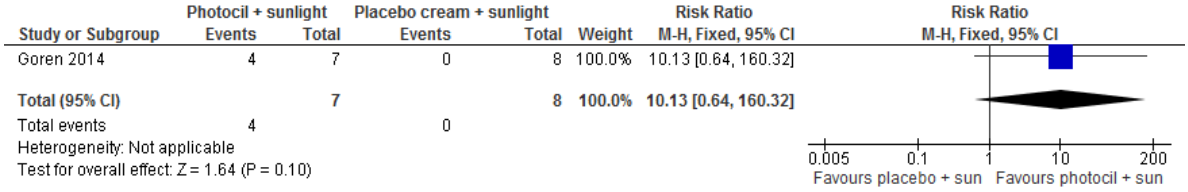
- Maintenance of gained repigmentation in **patients** at 6-month follow-up



Topical cream (Photocil) + natural sunlight vs. placebo + natural sunlight

Important outcomes

- Repigmentation ≥50% in **patients** at 3-month follow-up

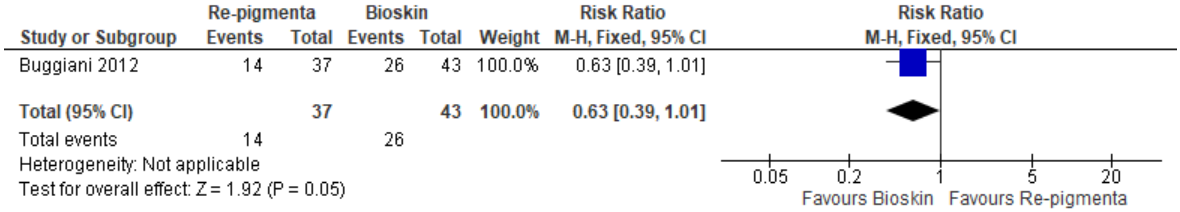


N.B. Change in scale

Re-pigmenta vs. Bioskin

Critical outcomes

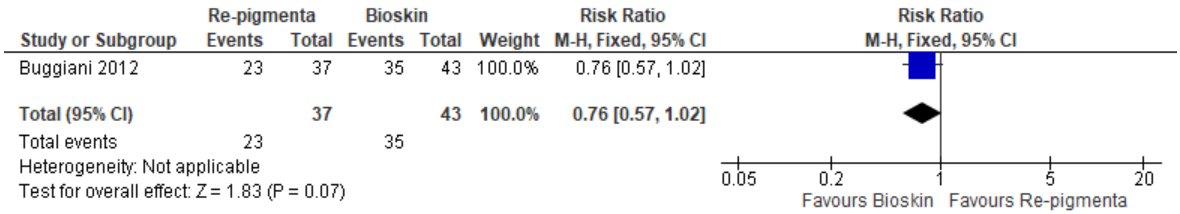
- Repigmentation ≥75% (>75%) in **patients** at 12 weeks (wks.) follow-up



N.B. Change in scale

Important outcomes

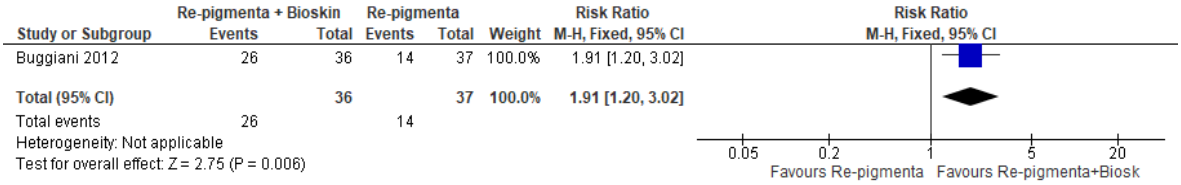
- Repigmentation ≥50% (>50%) in **patients** at 12 wks. follow-up



Re-pigmenta + Bioskin vs. Re-pigmenta

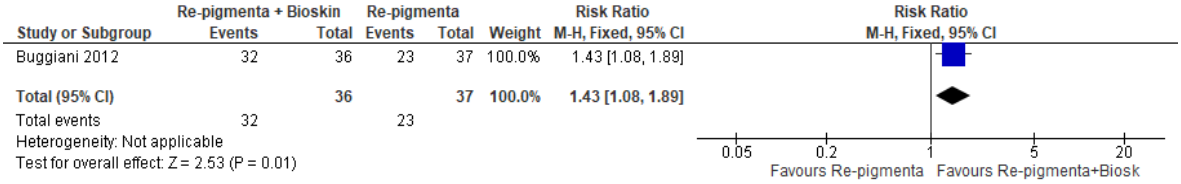
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 12 wks. follow-up



Important outcomes

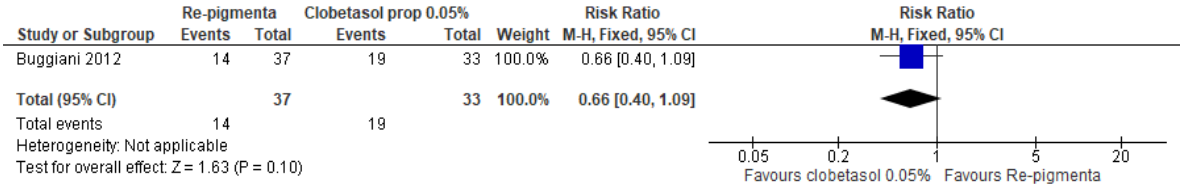
- Repigmentation ≥50% (>50%) in **patients** at 12 wks. follow-up



Re-pigmenta vs. Clobetasol propionate 0.05%

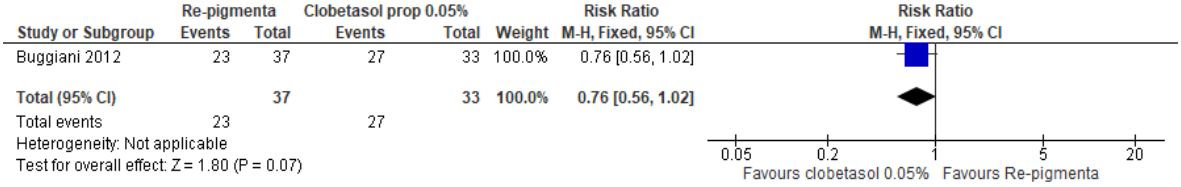
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 12 wks. follow-up



Important outcomes

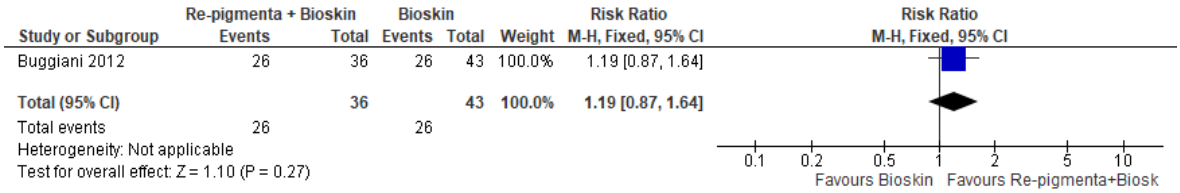
- Repigmentation ≥50% (>50%) in **patients** at 12 wks. follow-up



Repigmenta + Bioskin vs. Bioskin

Critical outcomes

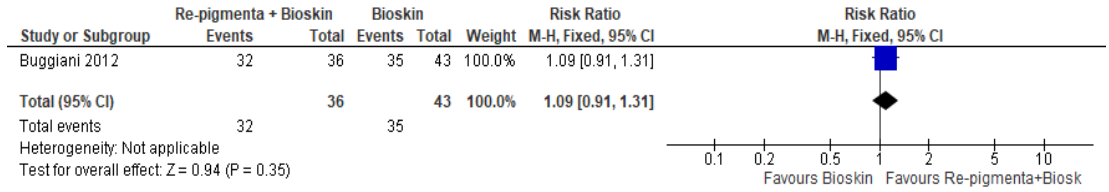
- Repigmentation ≥75% (>75%) in **patients** at 12 wks. follow-up



N.B. Change in scale

Important outcomes

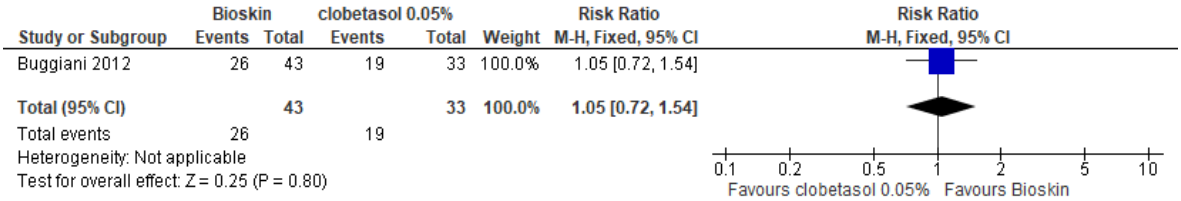
- Repigmentation ≥50% (>50%) in **patients** at 12 wks. follow-up



Bioskin vs. Clobetasol propionates 0.05%

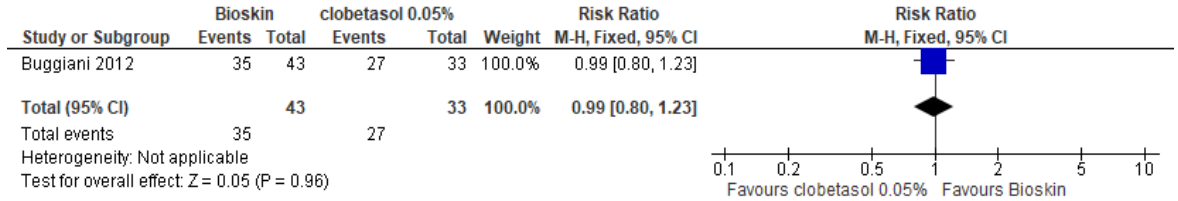
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 12 wks. follow-up



Important outcomes

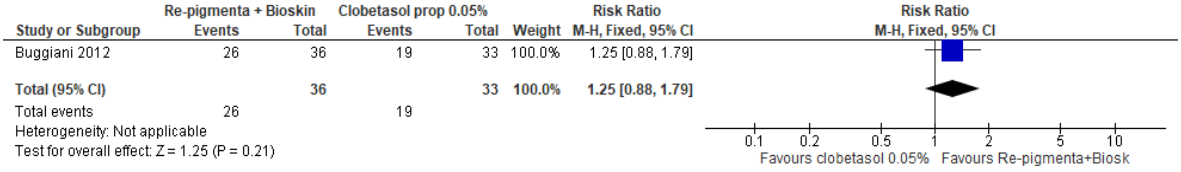
- Repigmentation ≥50% (>50%) in **patients** at 12 wks. follow-up



Re-pigmenta + Bioskin vs. Clobetasol propionate 0.05%

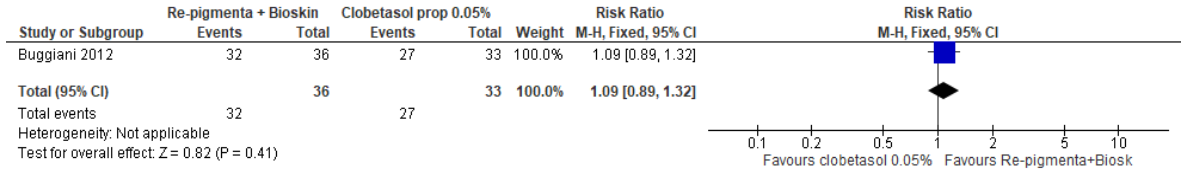
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 12 wks. follow-up



Important outcomes

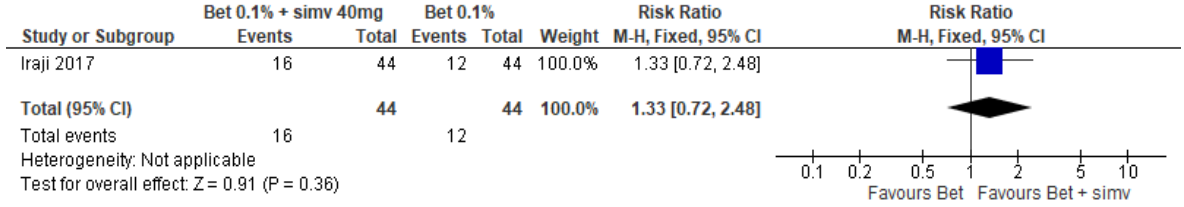
- Repigmentation ≥50% (>50%) in **patients** at 12 wks follow-up



Betamethasone valerate 0.1% + simvastatin 40mg vs. betamethasone valerate 0.1%

Important outcomes

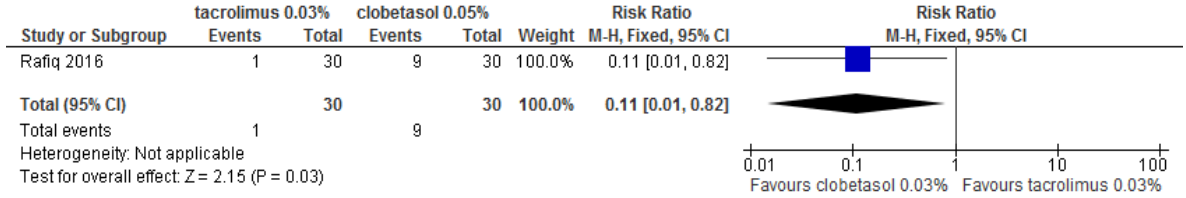
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Tacrolimus 0.03% vs. clobetasol 0.05%

Critical outcomes

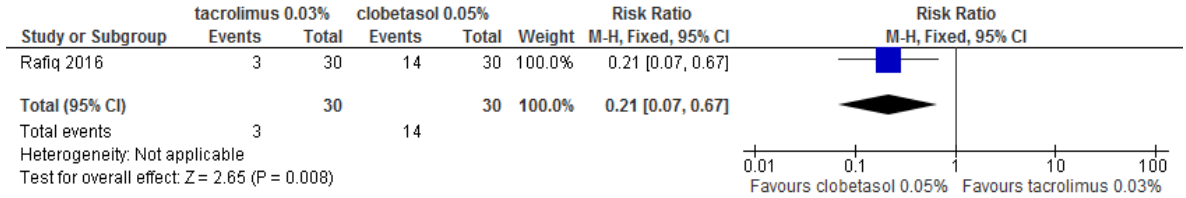
- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



N.B. Change in scale

Important outcomes

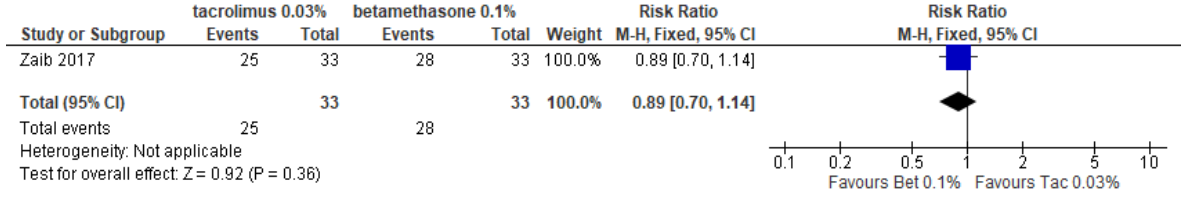
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Tacrolimus 0.03% vs. betamethasone valerate 0.1%

Important outcomes

- Repigmentation ≥50% in **patients** at 3-month follow-up



N.B. Change in scale

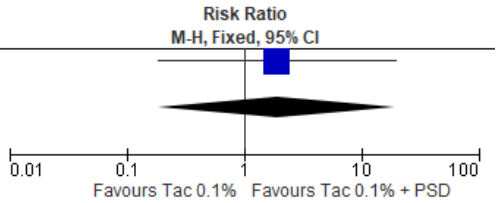
Tacrolimus 0.1% + PSD (pseudocatalase/superoxide) vs. tacrolimus 0.1%

Critical outcomes

- Repigmentation ≥ 75% (> 75%) at 9-month follow-up

Study or Subgroup	Tac 0.1% + PSD Events	Total	Tac 0.1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alshiyab 2020	2	25	1	24	100.0%	1.92 [0.19, 19.82]
Total (95% CI)		**25**		**24**	**100.0%**	**1.92 [0.19, 19.82]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)



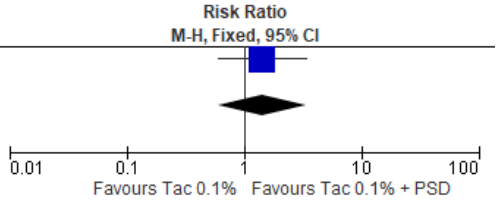
N.B. Change in scale

Important outcomes

- Repigmentation ≥ 50% (> 50%) at 9-month follow-up

Study or Subgroup	Tac 0.1% + PSD Events	Total	Tac 0.1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alshiyab 2020	9	25	6	24	100.0%	1.44 [0.60, 3.43]
Total (95% CI)		**25**		**24**	**100.0%**	**1.44 [0.60, 3.43]**
Total events	9		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



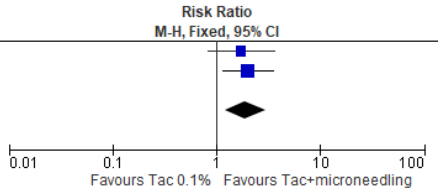
Tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%

Critical outcomes

- Repigmentation ≥ 75% (> 75%) in **patients** at 3-month post-treatment follow-up

Study or Subgroup	Tac 0.1% + microneedling Events	Total	Tac 0.1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ebrahim 2020	12	24	7	24	41.2%	1.71 [0.82, 3.60]
Ebrahim J Cosmet Dermatol 2020	20	30	10	30	58.8%	2.00 [1.14, 3.52]
Total (95% CI)		**54**		**54**	**100.0%**	**1.88 [1.20, 2.95]**
Total events	32		17			

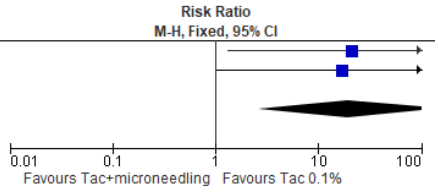
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.76 (P = 0.006)



- Pain in **patients** at 3-month post-treatment follow-up

Study or Subgroup	Tac 0.1% + microneedling Events	Total	Tac 0.1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ebrahim 2020	10	24	0	24	50.0%	21.00 [1.30, 339.29]
Ebrahim J Cosmet Dermatol 2020	8	30	0	30	50.0%	17.00 [1.03, 281.91]
Total (95% CI)		**54**		**54**	**100.0%**	**19.00 [2.63, 137.02]**
Total events	18		0			

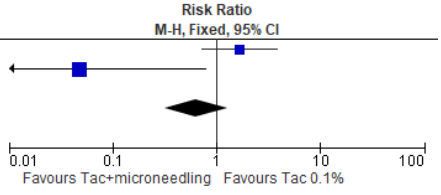
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)



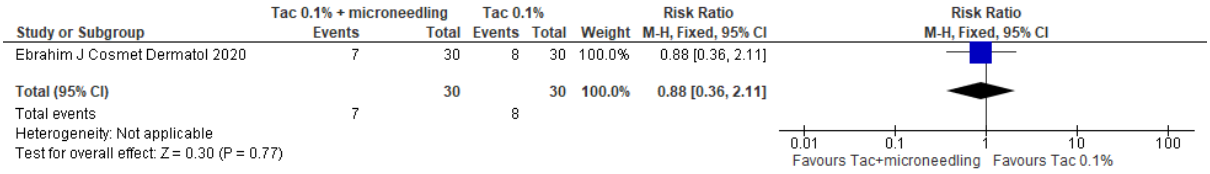
- Itching in **patients** at 3-month post-treatment follow-up

Study or Subgroup	Tac 0.1% + microneedling Events	Total	Tac 0.1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ebrahim 2020	10	24	6	24	36.4%	1.67 [0.72, 3.86]
Ebrahim J Cosmet Dermatol 2020	0	30	10	30	63.6%	0.05 [0.00, 0.78]
Total (95% CI)		**54**		**54**	**100.0%**	**0.64 [0.32, 1.27]**
Total events	10		16			

Heterogeneity: Chi² = 8.37, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 1.28 (P = 0.20)

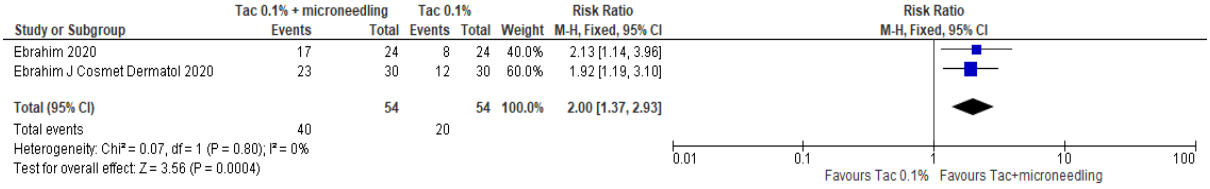


- Erythema in **patients** at 3-month post-treatment follow-up



Important outcomes

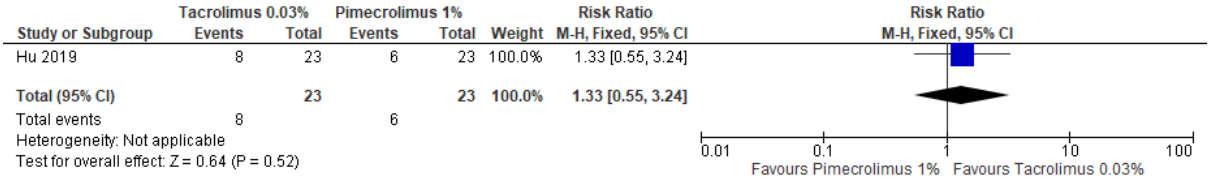
- Repigmentation ≥ 50% (> 50%) in **patients** at 3-month post-treatment follow-up



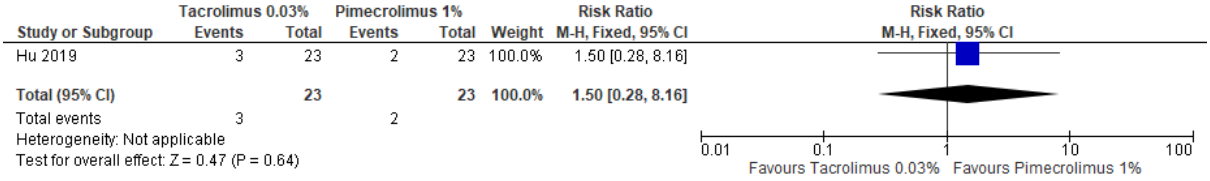
Tacrolimus 0.03% vs. pimecrolimus 1%

Critical outcomes

- Repigmentation ≥ 75% (>75%) in **infants** (< 2 years) at 6-month follow-up

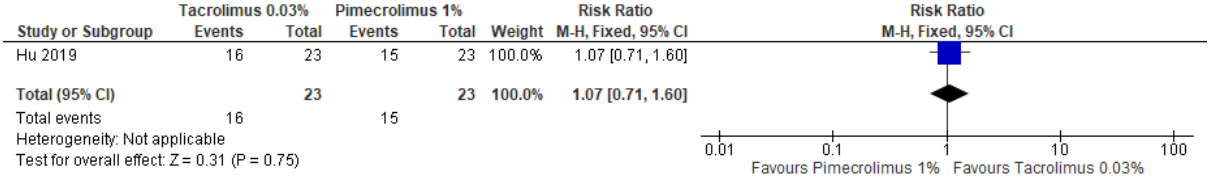


- Mild redness and scratch in **infants** (<2 years) at 6-month follow-up



Important outcomes

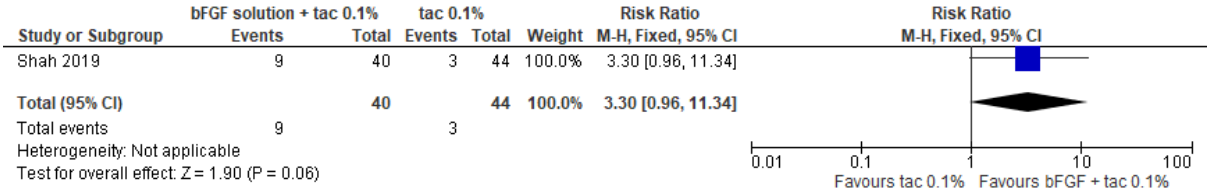
- Repigmentation ≥ 50% (>50%) in **infants** (<2 years) at 6-month follow-up



bFGF related decapeptide solution + tacrolimus 0.1% vs. tacrolimus 0.1%

Important outcomes

- Repigmentation ≥ 50% (>50%) in **patients** at 12-month follow-up

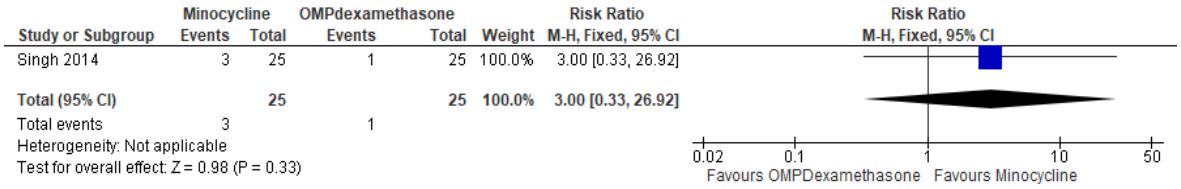


Systemic Therapies

Minocycline (100 mg/day) vs. oral minipulse (OMP) dexamethasone (2.5 mg)

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



N.B. Change in scale

- Adverse effects in **patients** at 6-month follow-up

N.B. Change in scale

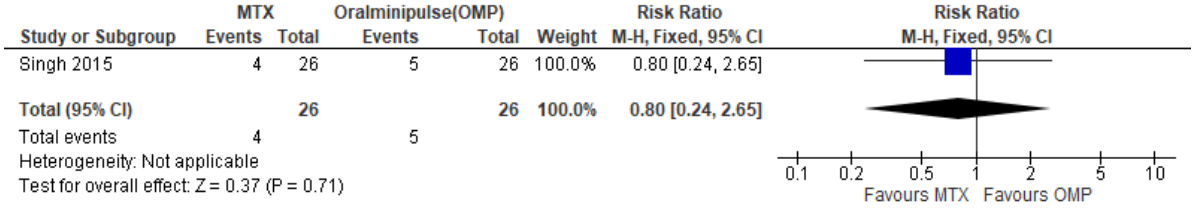
Important outcomes

- **Patients** without new lesions at 6-month follow-up

Methotrexate (MTX) 10mg weekly vs. OMP (dexamethasone) 2.5mg taken on two consecutive days in a week.

Critical outcomes

- Adverse effects in **patients** at 6-month follow-up

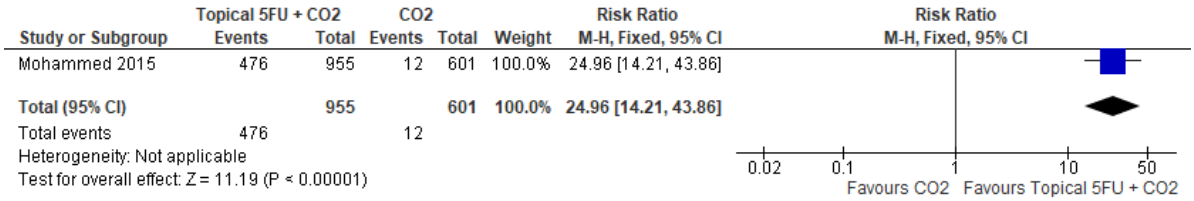


Light and laser Therapies

CO_2 laser + topical 5-FU vs. CO_2 laser

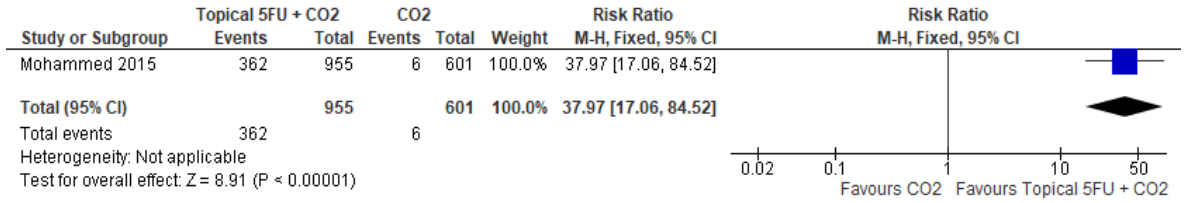
Critical outcomes

- Repigmentation ≥75% in **lesions** on **hands and feet** at 6-month follow-up



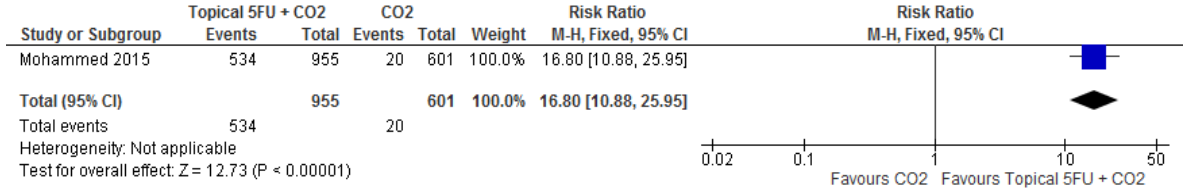
N.B. Change in scale

- Complete repigmentation (100%) in **lesions** on **hands and feet** at 6-month follow-up



Important outcomes

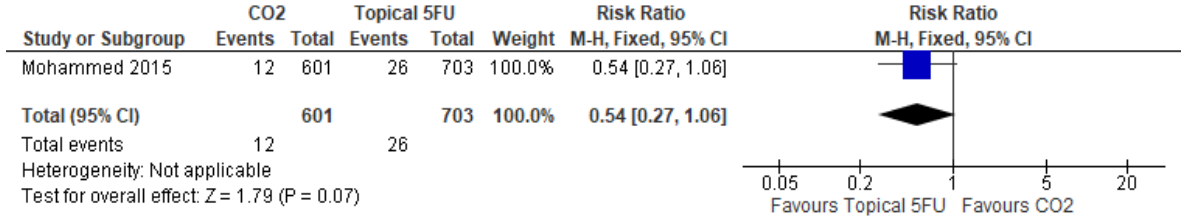
- Repigmentation ≥50% in **lesions** on **hands and feet** at 6-month follow-up



CO_2 laser vs. topical 5FU

Critical outcomes

- Repigmentation ≥75% in **lesions** on **hands and feet** at 6-month follow-up



N.B. Change in scale. Complete repigmentation (100%) in **lesions** **hands and feet** at 6-month follow-up

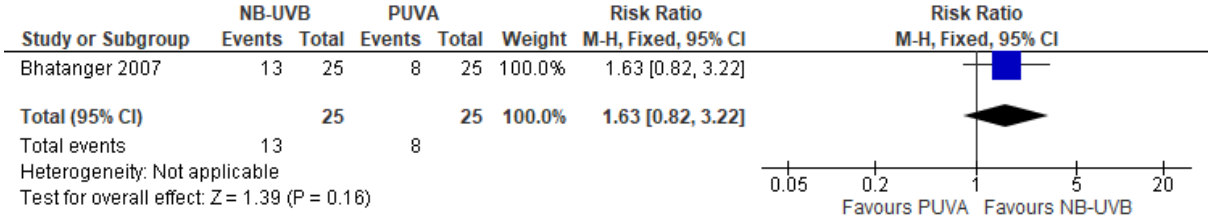
Important outcomes

- Repigmentation ≥50% in **lesions** on **hands and feet** at 6-month follow-up

NB-UVB vs. PUVA

Important outcomes

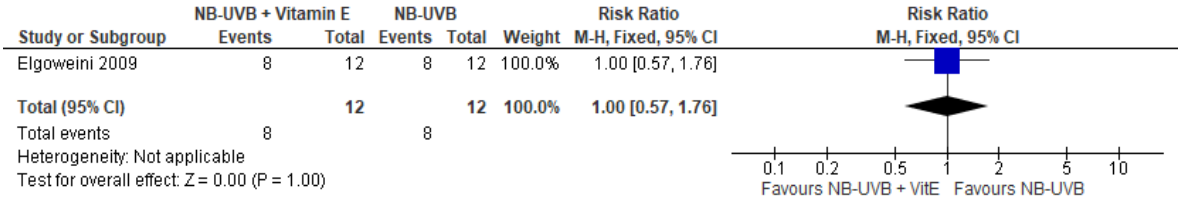
- Repigmentation in **patients** ≥50% (>50%) at 6-month follow-up



NB-UVB + vitamin E vs. NB-UVB

Critical outcomes

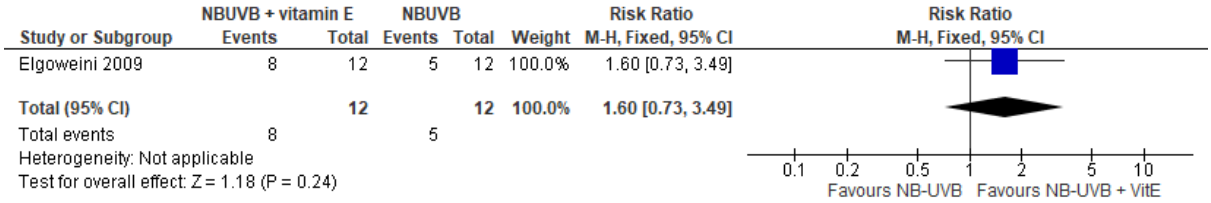
- Mild erythema in **patients** at 6-month follow-up



N.B. Change in scale

Important outcomes

- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up

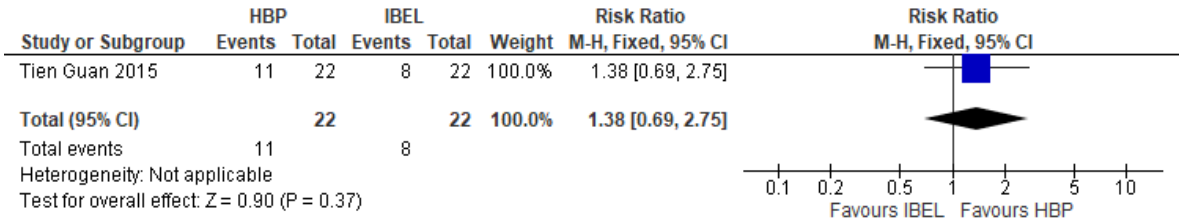


N.B. Change in scale

Hand-held, home-based phototherapy (HBP) vs. institution-based excimer lamp (IBEL)

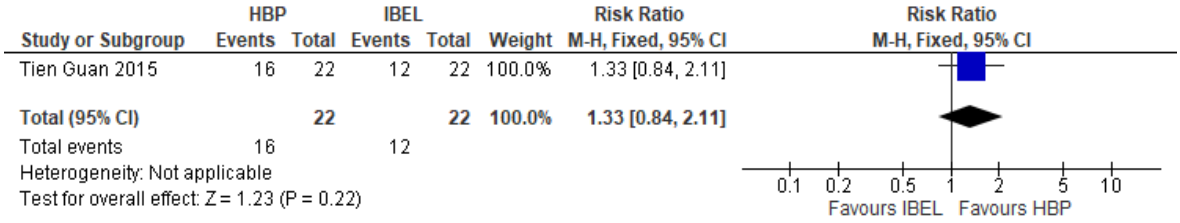
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



Important outcomes

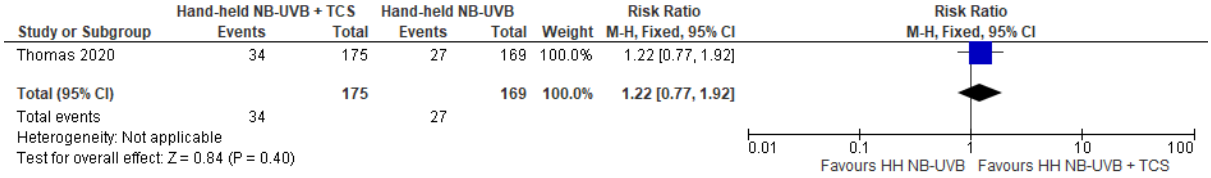
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



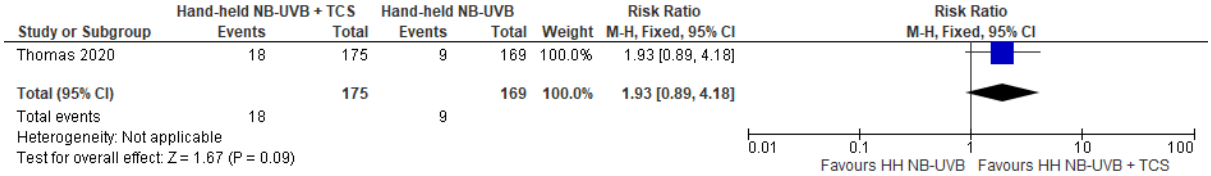
Hand-held NB-UVB + TCS (topical corticosteroid: mometasone furoate 0.1% ointment + dummy hand-held NB-UVB) vs. Hand-held NB-UVB

Critical outcomes

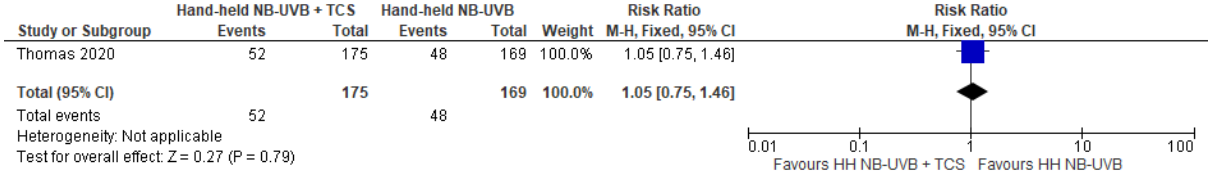
- Treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9 months in **patients**



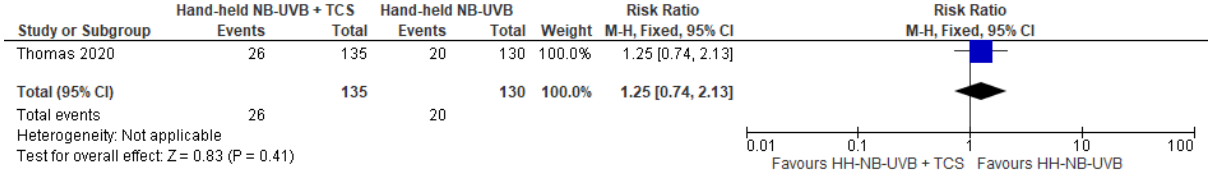
- Repigmentation ≥75% at 9 months in **patients**



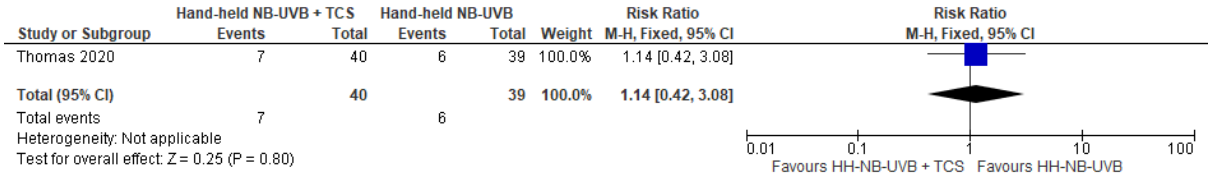
- Treatment-related adverse events at 9 months in **patients**



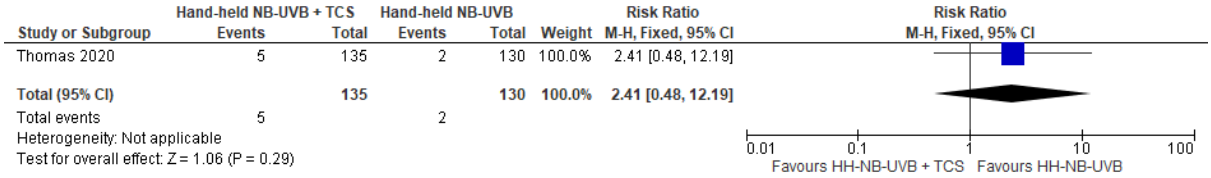
- Erythema (Grade 3 and 4) at 9 months in **adults**



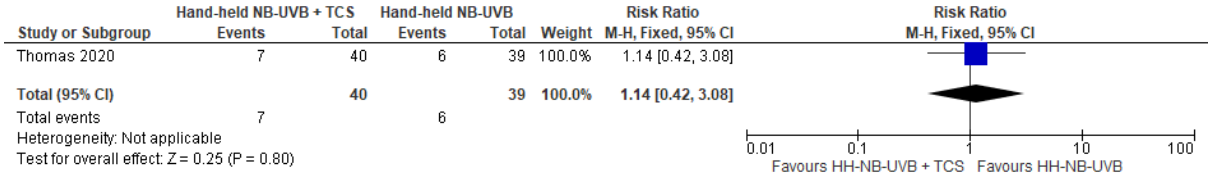
- Erythema (Grade 3 and 4) at 9 months in **children**



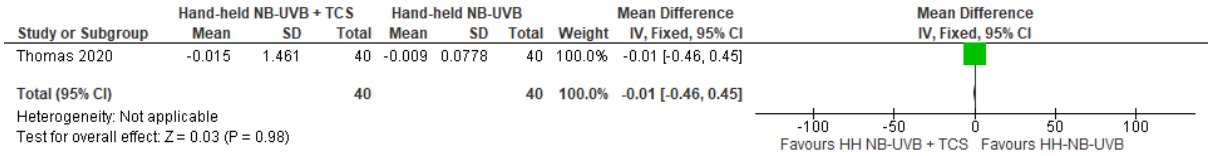
- Skin thinning at 9 months in **adults**



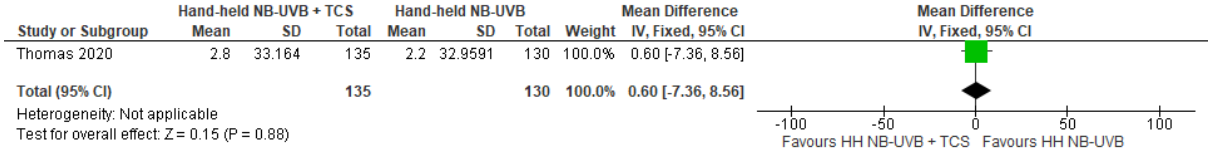
- Skin thinning at 9 months in **children**



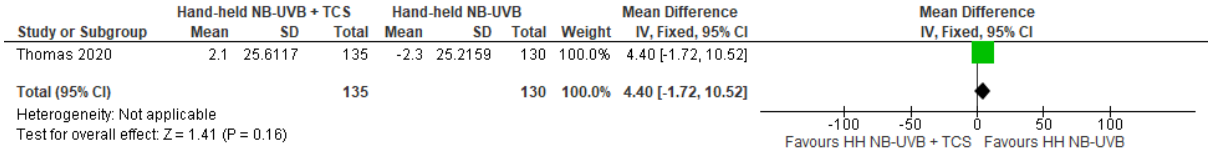
- Change in CHU9D at 9-months in **children**



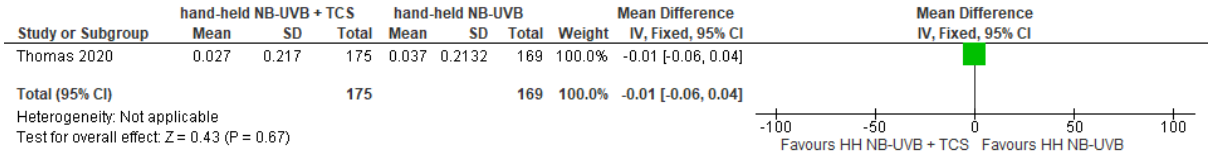
- Change in VitiQoL at 21-month follow-up in **adults**



- Change in Skindex 29 at 21-month follow-up in **adults**

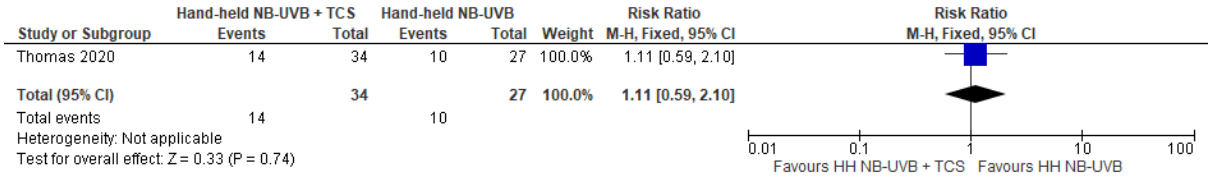


- Change in EQ-5D in **patients** at 9 months



Important outcomes

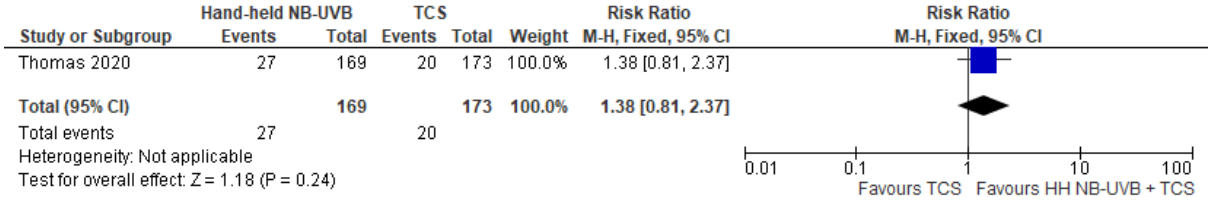
- Participant reported loss of treatment response at 21-month follow-up in those with treatment success at 9 months



Hand-held home-based NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)

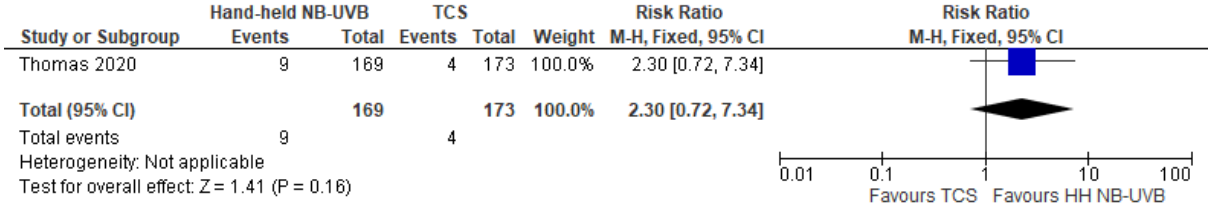
<u>Critical outcomes</u>

- Patient reported treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9-month follow-up

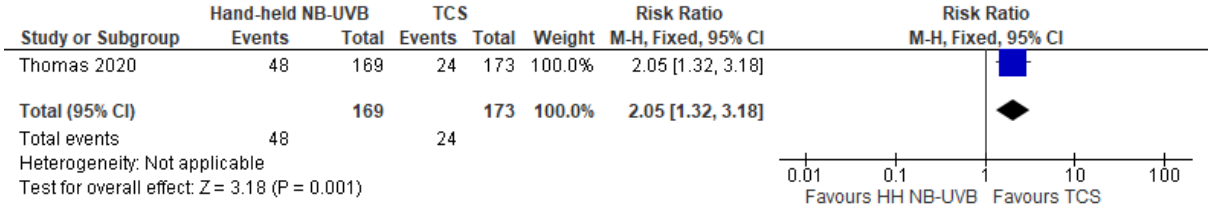


N.B. Change in scale

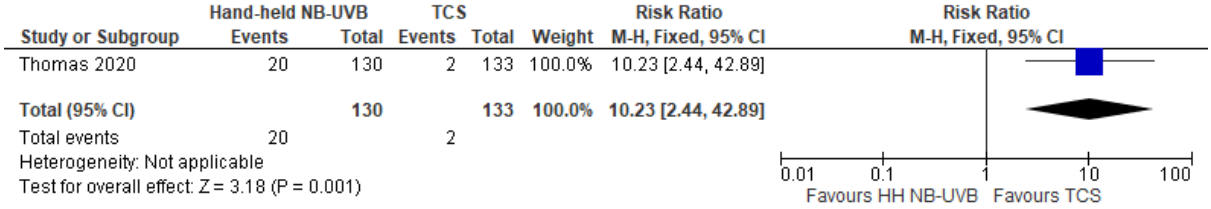
- Repigmentation ≥75% in **patients** at 9-month follow-up



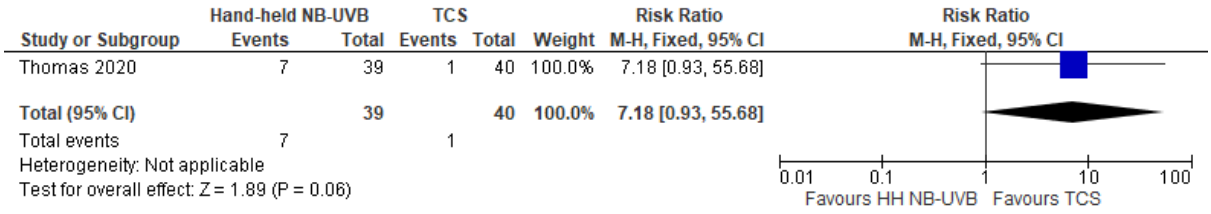
- Treatment-related adverse events in **patients** at 9-months



- Erythema (Grade 3 and 4) at 9 months in **adults**

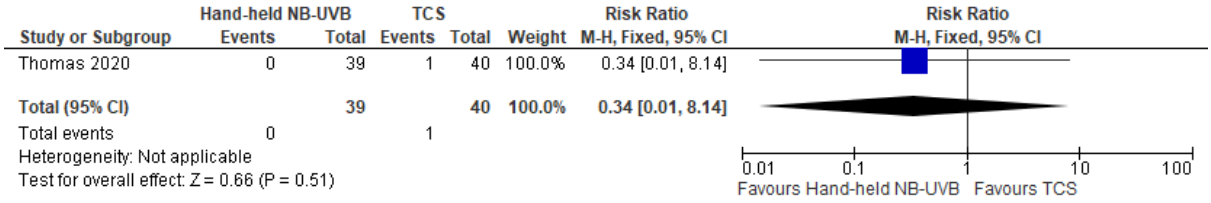


- Erythema (Grade 3 and 4) at 9 months in **children**

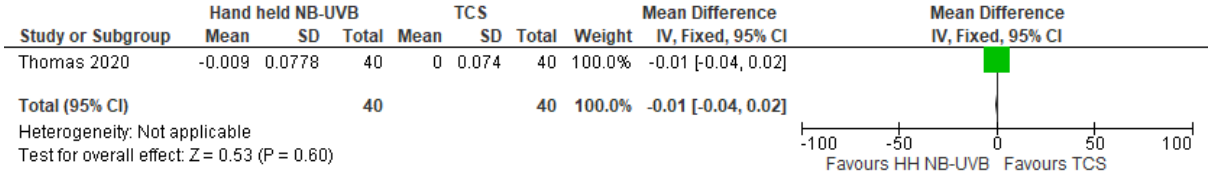


- Skin thinning at 9 months in **adults**

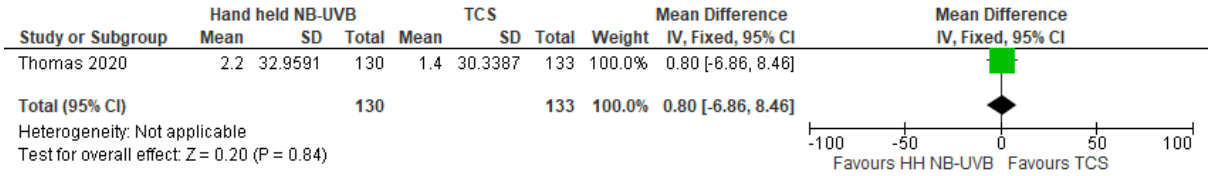
- Skin thinning at 9 months in **children**



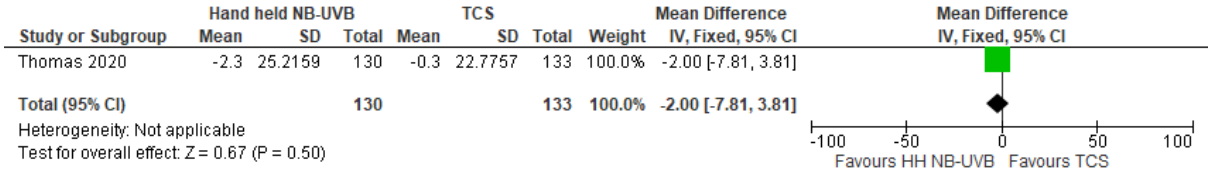
- Change in CHU9D at 9-months in **children**



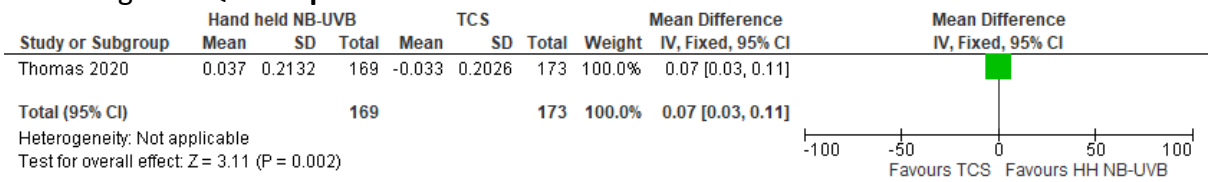
- Change in VitiQoL at 21-month follow-up in **adults**



- Change in Skindex 29 at 21-month follow-up in **adults**

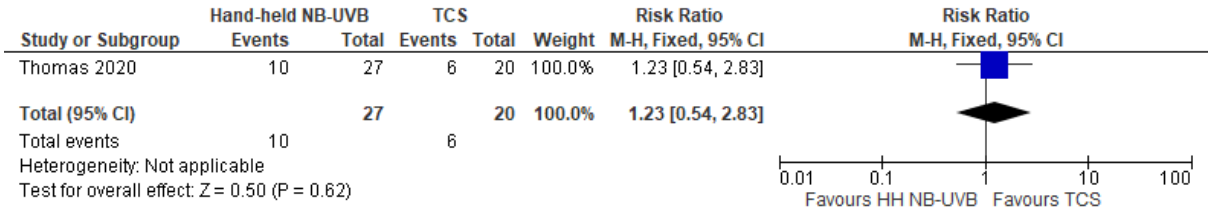


- Change in EQ-5D in **patients** at 9 months



<u>Important outcomes</u>

- Participant reported loss of treatment response at 21-month follow-up in those with treatment success at 9 months



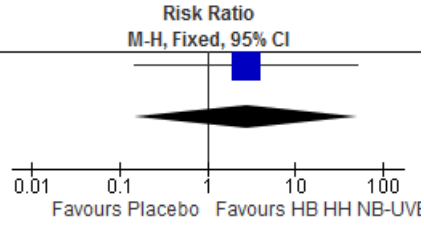
Hand-held home-based NB-UVB vs. placebo

Critical outcomes

- Repigmentation ≥75% in **patients** at 16-week follow-up

Study or Subgroup	HB HH NB-UVB Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eleftheriadou 2014	2	19	0	10	100.0%	2.75 [0.14, 52.33]
Total (95% CI)		**19**		**10**	**100.0%**	**2.75 [0.14, 52.33]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

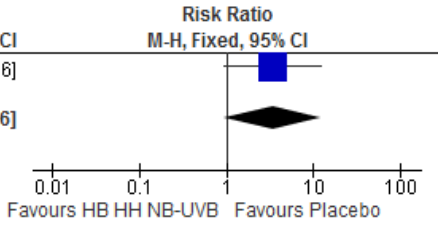


N.B. Change in scale

- Erythema in **patients** at 16-week follow-up

Study or Subgroup	HB HH NB-UVB Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eleftheriadou 2014	13	19	2	10	100.0%	3.42 [0.95, 12.26]
Total (95% CI)		**19**		**10**	**100.0%**	**3.42 [0.95, 12.26]**
Total events	13		2			

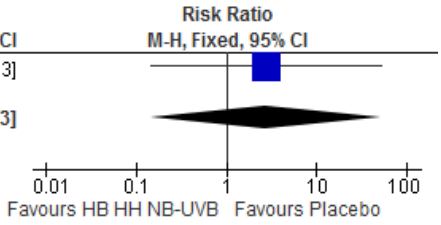
Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)



- Pruritus in **patients** at 16-week follow-up

Study or Subgroup	HB HH NB-UVB Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eleftheriadou 2014	2	19	0	10	100.0%	2.75 [0.14, 52.33]
Total (95% CI)		**19**		**10**	**100.0%**	**2.75 [0.14, 52.33]**
Total events	2		0			

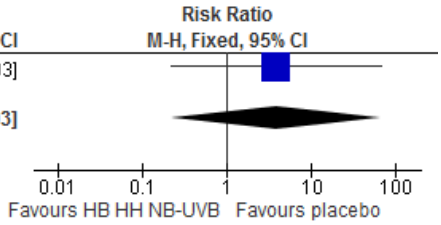
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



- Hyperpigmentation in **patients** at 16-week follow-up

Study or Subgroup	HB HH NB-UVB Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eleftheriadou 2014	3	19	0	10	100.0%	3.85 [0.22, 67.93]
Total (95% CI)		**19**		**10**	**100.0%**	**3.85 [0.22, 67.93]**
Total events	3		0			

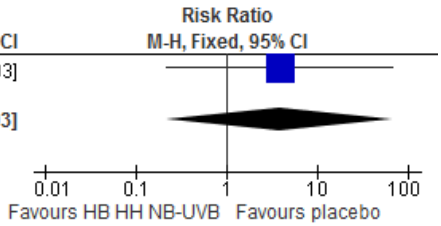
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)



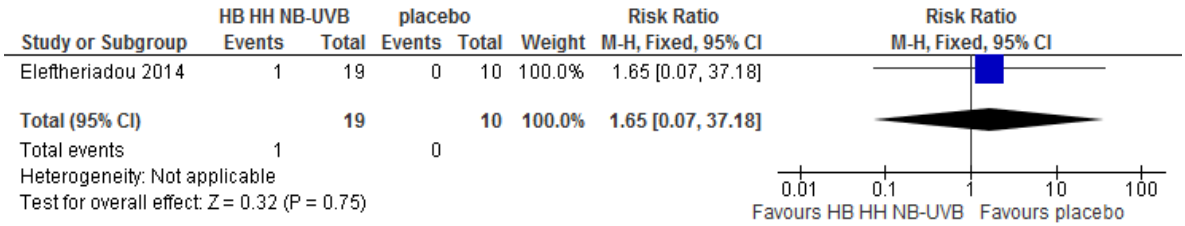
- Dry skin in **patients** at 16-week follow-up

Study or Subgroup	HB HH NB-UVB Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eleftheriadou 2014	3	19	0	10	100.0%	3.85 [0.22, 67.93]
Total (95% CI)		**19**		**10**	**100.0%**	**3.85 [0.22, 67.93]**
Total events	3		0			

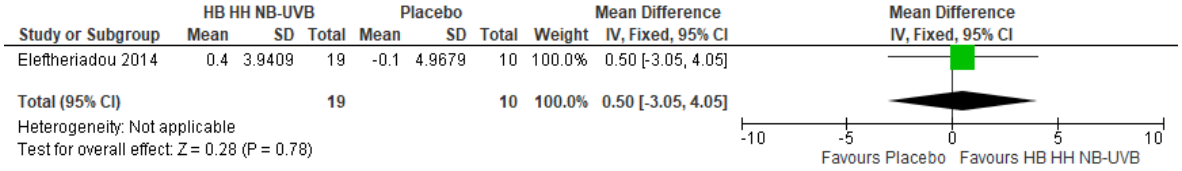
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)



- Cold sores in **patients** at 16-week follow-up



- QoL (DLQI) of **patients** at 16-week follow-up



N.B. Change in scale

Important outcomes

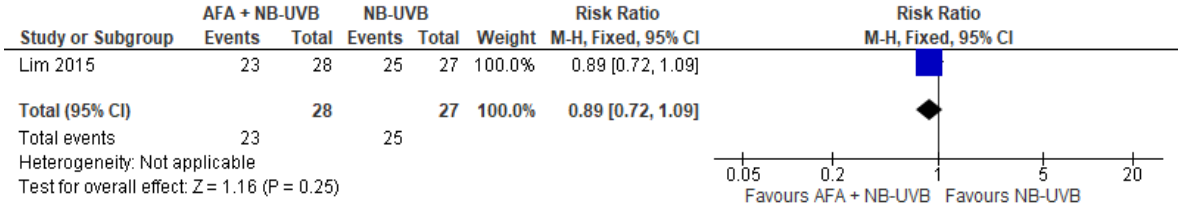
- Cessation of spreading of vitiligo **lesions** at 16-week follow-up

N.B. Change in scale

Afamelanotide implant + NB-UVB vs. NB-UVB

Critical outcomes

- Adverse events in **patients** at 6-month follow-up

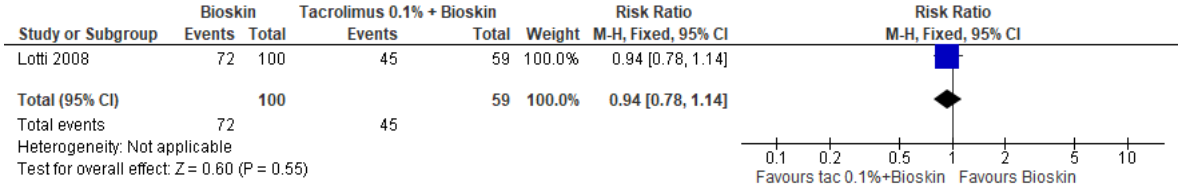


N.B. Change in scale

Bioskin vs. 0.1% tacrolimus + Bioskin

Critical outcomes

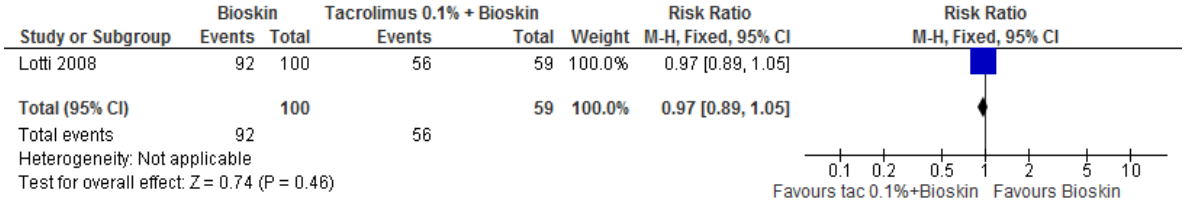
- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



N.B. Change in scale

Important outcomes

- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



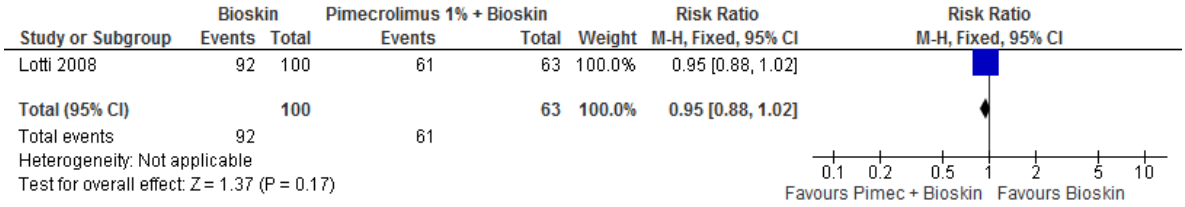
Bioskin vs. 1% pimecrolimus + Bioskin

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up

Important outcomes

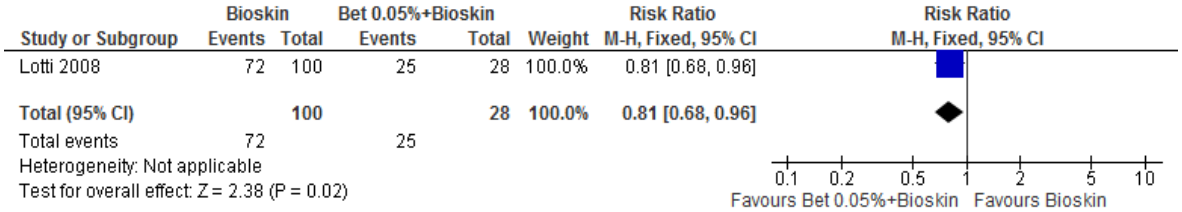
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Bioskin vs. betamethasone dipropionate 0.05% + Bioskin

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



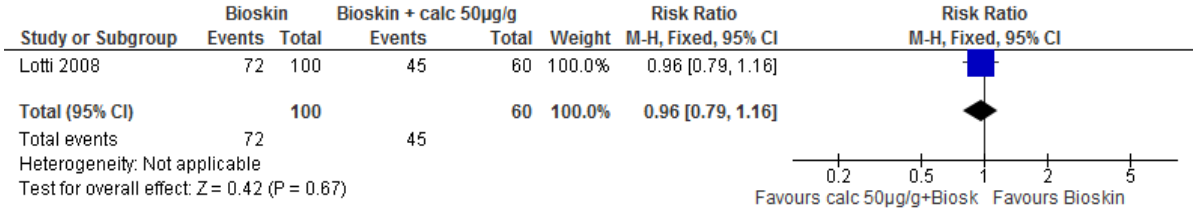
Important outcomes

- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up

Bioskin vs. calcipotriol ointment 50 µg/g + Bioskin

Critical outcomes

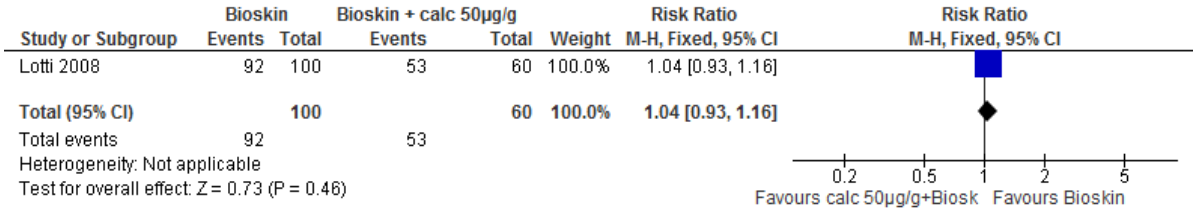
- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



N.B. Change in scale

Important outcomes

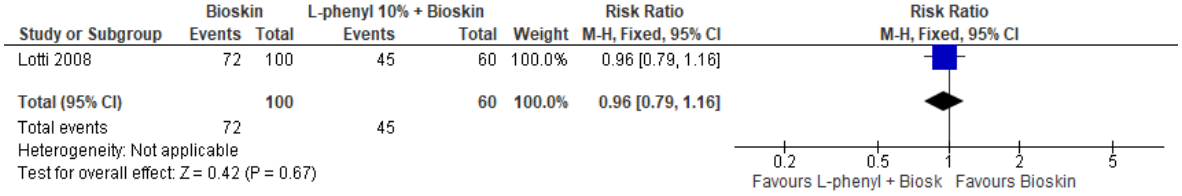
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Bioskin vs. 10% L-phenylalanine + Bioskin

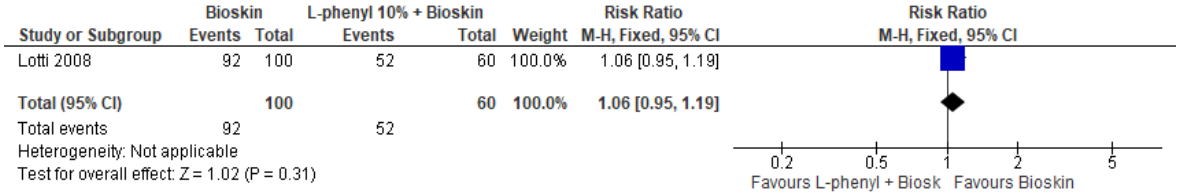
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



Important outcomes

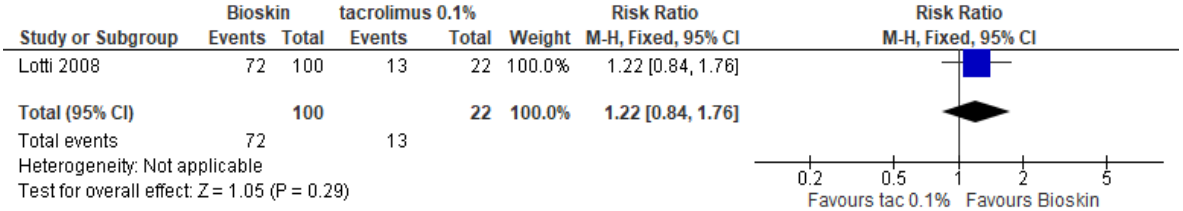
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Bioskin vs. 0.1% tacrolimus

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up

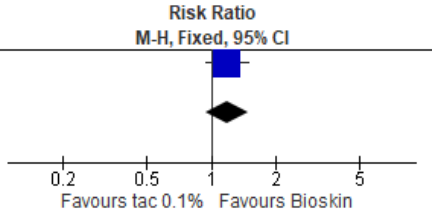


Important outcomes

- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up

Study or Subgroup	Bioskin Events	Total	tacrolimus 0.1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lotti 2008	92	100	17	22	100.0%	1.19 [0.94, 1.50]
Total (95% CI)		**100**		**22**	**100.0%**	**1.19 [0.94, 1.50]**
Total events	92		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)



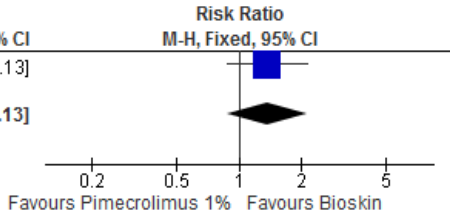
Bioskin vs. 1% pimecrolimus

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up

Study or Subgroup	Bioskin Events	Total	Pimecrolimus 1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lotti 2008	72	100	10	19	100.0%	1.37 [0.88, 2.13]
Total (95% CI)		**100**		**19**	**100.0%**	**1.37 [0.88, 2.13]**
Total events	72		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

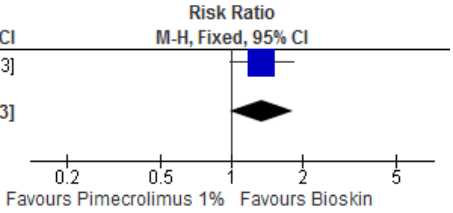


Important outcomes

- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up

Study or Subgroup	Bioskin Events	Total	Pimecrolimus 1% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lotti 2008	92	100	13	19	100.0%	1.34 [0.99, 1.83]
Total (95% CI)		**100**		**19**	**100.0%**	**1.34 [0.99, 1.83]**
Total events	92		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)



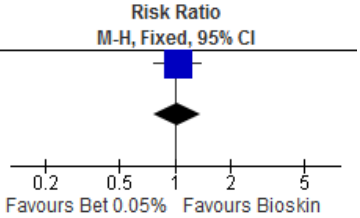
Bioskin vs. betamethasone dipropionate 0.05%

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up

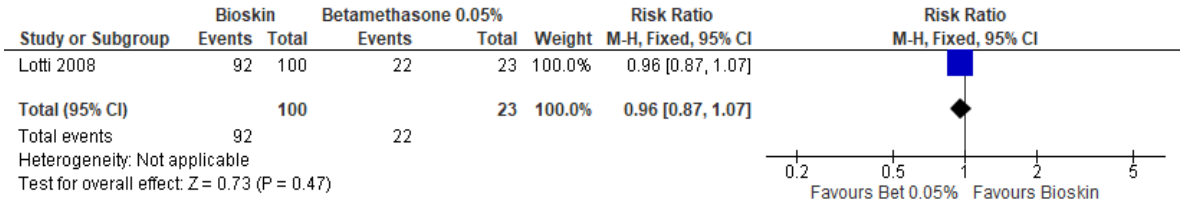
Study or Subgroup	Bioskin Events	Total	Betamethasone 0.05% Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lotti 2008	72	100	16	23	100.0%	1.03 [0.77, 1.39]
Total (95% CI)		**100**		**23**	**100.0%**	**1.03 [0.77, 1.39]**
Total events	72		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



Important outcomes

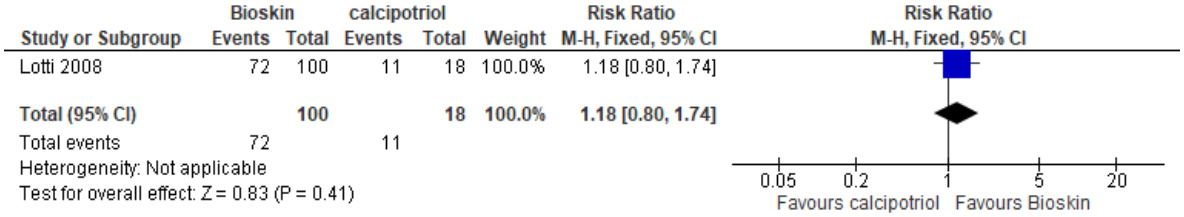
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Bioskin vs. calcipotriol 50 µg/g

Critical outcomes

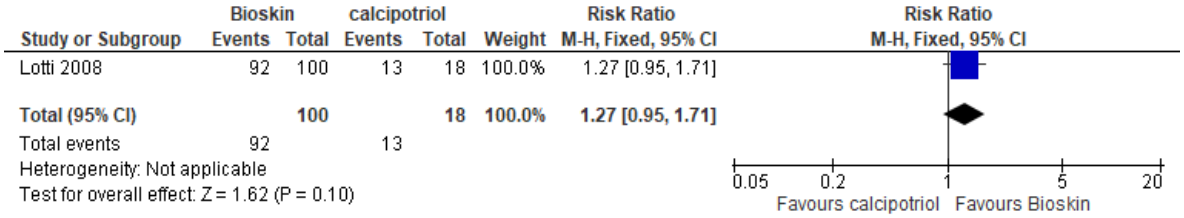
- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up



N.B. Change in scale

Important outcomes

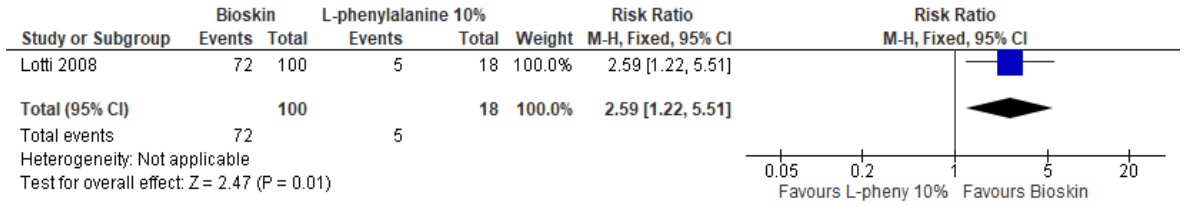
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Bioskin vs. 10% L-phenylalanine

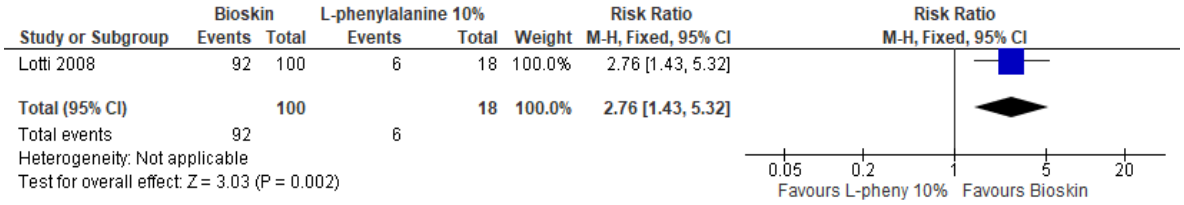
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up.



Important outcomes

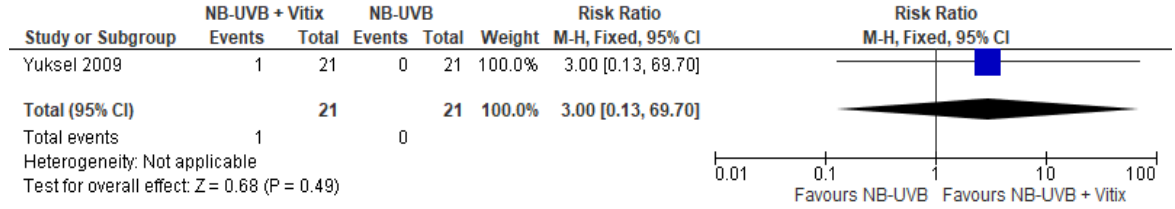
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



NB-UVB + catalase-superoxide (vitix gel) vs. NB-UVB

Critical outcomes

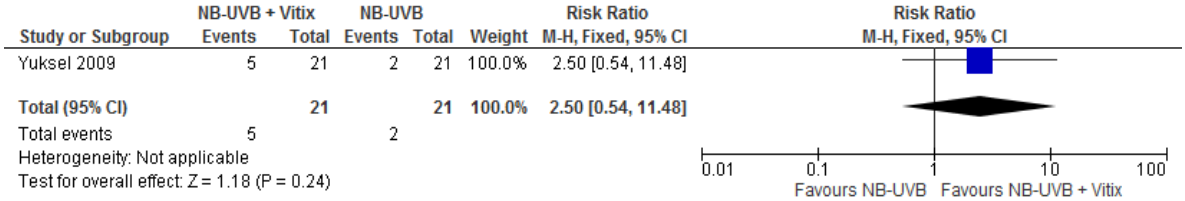
- Repigmentation ≥75% (>75%) in **lesions** at 6-month follow-up.



N.B. Change in scale

Important outcomes

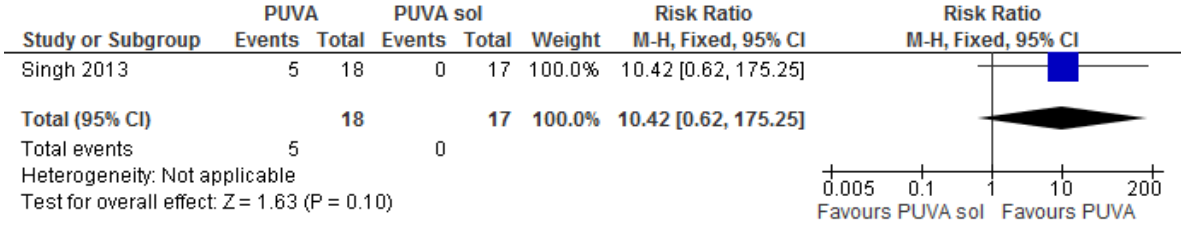
- Repigmentation ≥50% (>50%) in **lesions** at 6-month follow-up



PUVA vs. PUVA sol

Critical outcomes

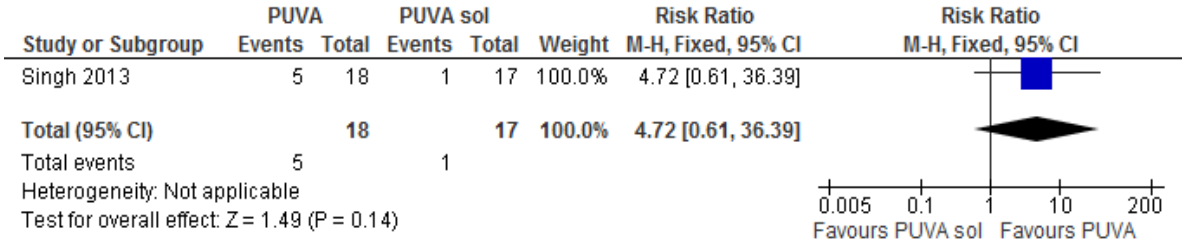
- Repigmentation ≥75% (>75%) in **patients** at 36 wks. follow-up



N.B. Change in scale

Important outcomes

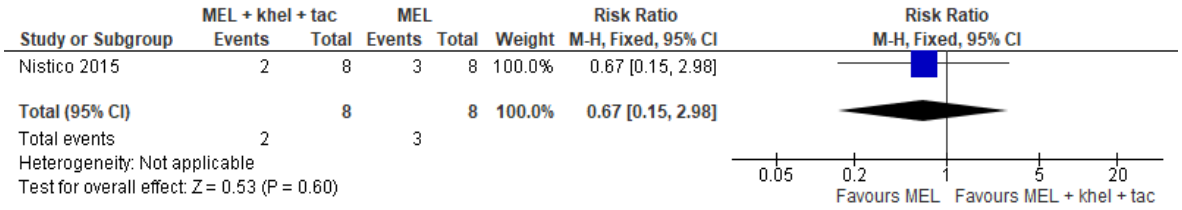
- Repigmentation ≥50% (>50%) in **patients** at 36 wks. follow-up



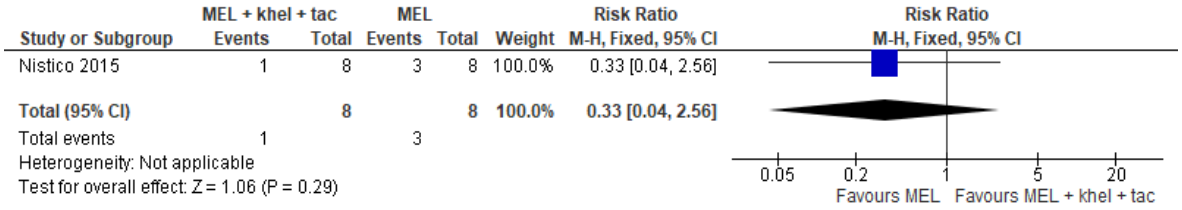
Monochromatic excimer light (MEL) + khellin + tacrolimus 0.1% vs. MEL

Critical outcomes

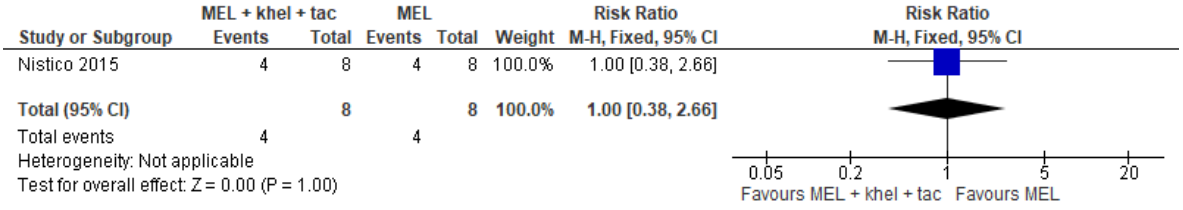
- Repigmentation ≥ 75% (75%) in **patients** at 3-month follow-up



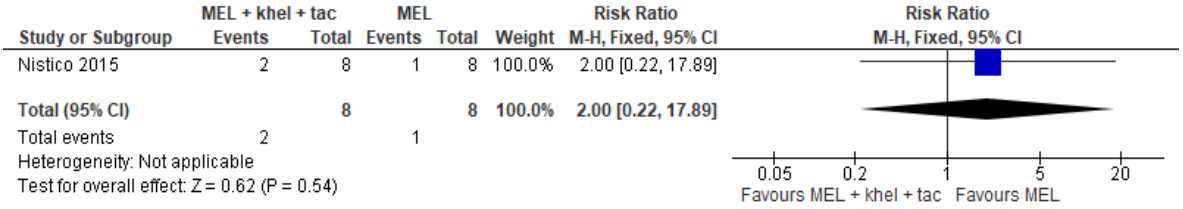
N.B. Change in scale. Complete repigmentation (100%) in **patients** at 3-month follow-up



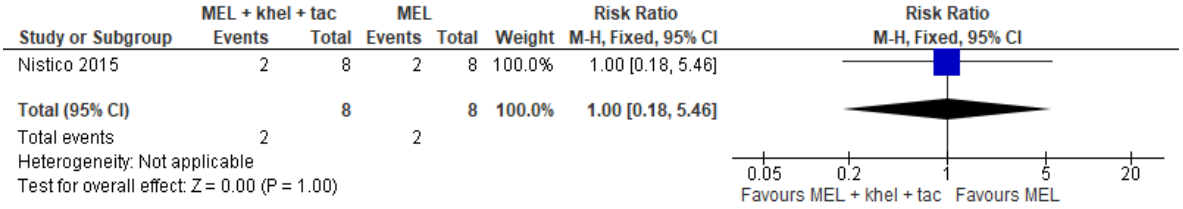
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

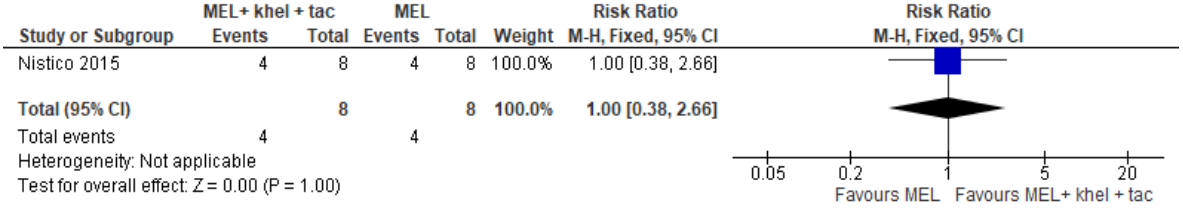


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



<u>Important outcomes</u>

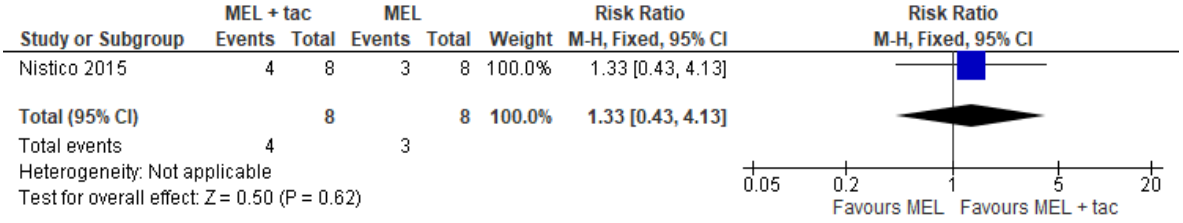
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



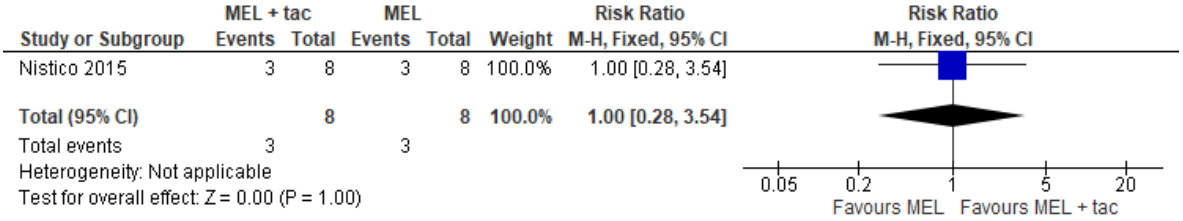
MEL + tacrolimus vs. MEL

<u>Critical outcomes</u>

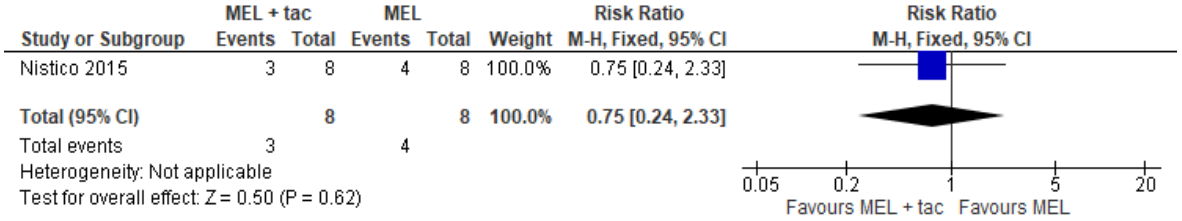
- Repigmentation ≥ 75% (>75%) in **patients** at 3-month follow-up



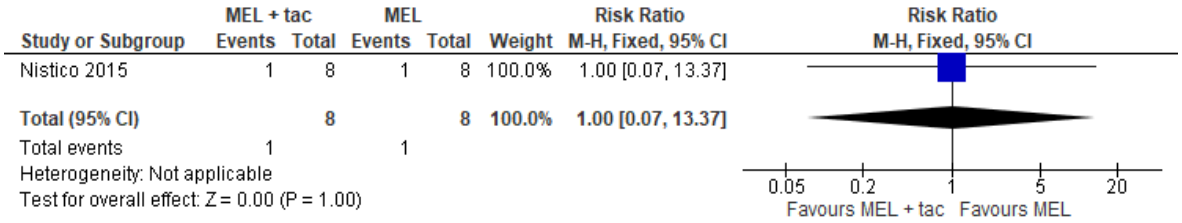
N.B. Complete repigmentation (100%) in **patients** at 3-month follow-up



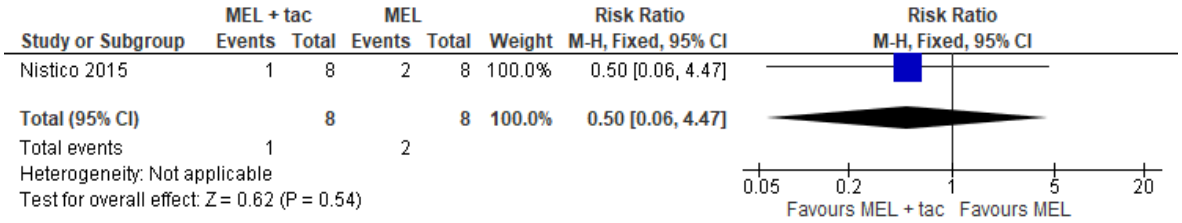
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

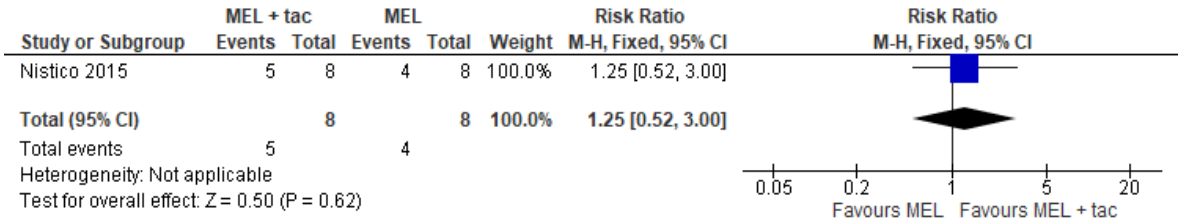


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



<u>Important outcomes</u>

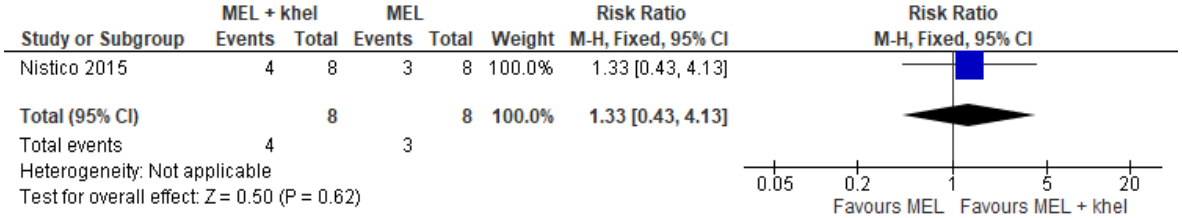
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



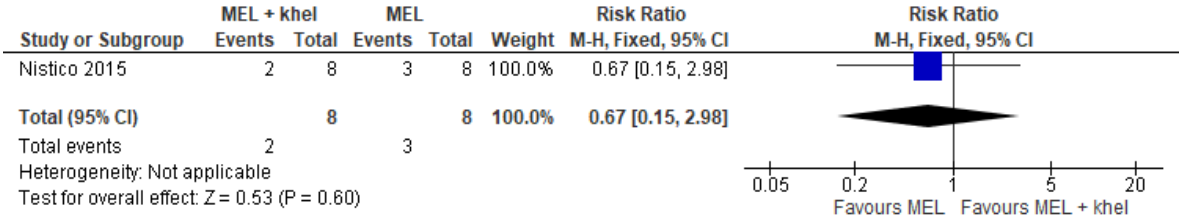
MEL + khellin vs. MEL

<u>Critical outcomes</u>

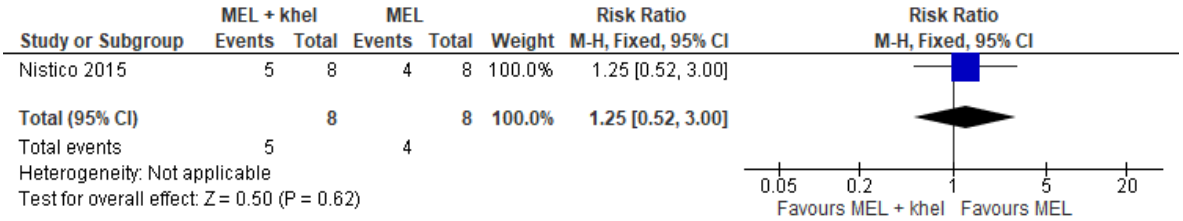
- Repigmentation ≥ 75% (>75%) in **patients** at 3-month follow-up



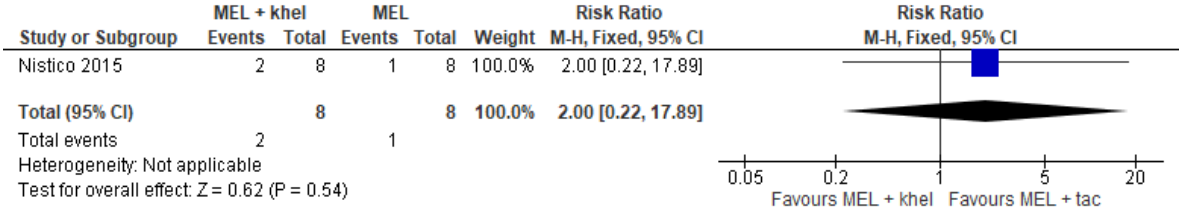
N.B. Complete repigmentation (100%) in **patients** at 3-month follow-up



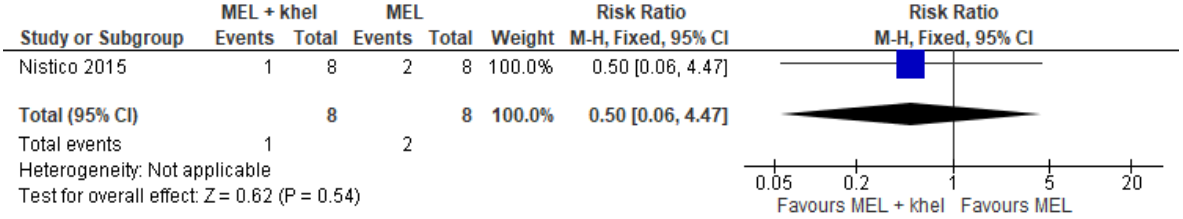
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

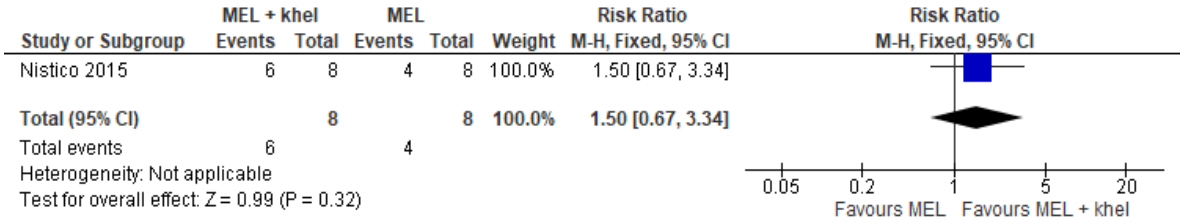


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



Important outcomes

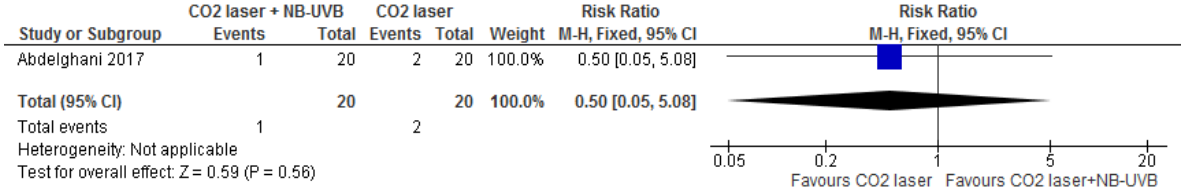
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



CO_2 laser + NB-UVB vs. CO_2

Critical outcomes

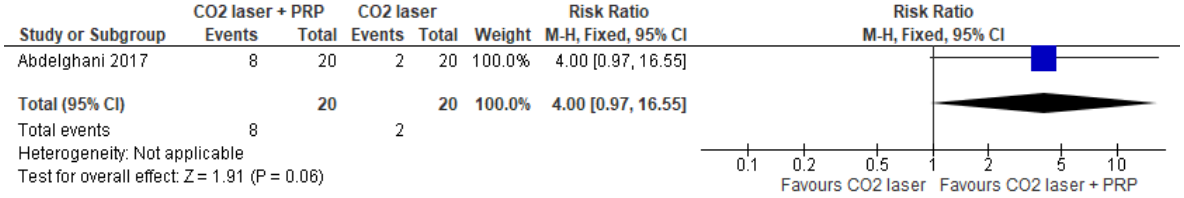
- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up



CO_2 laser + Platelet rich plasma (PRP) vs. CO_2 laser

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up

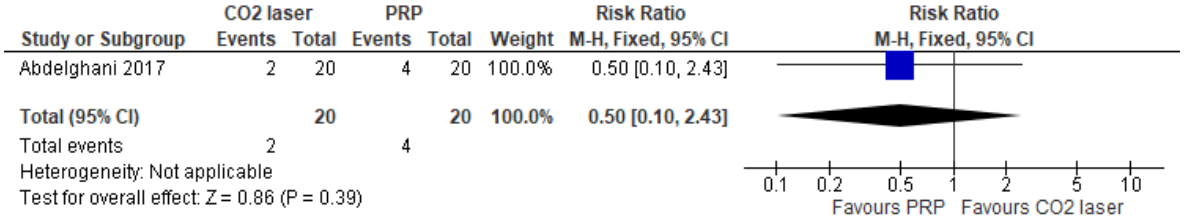


N.B. Change in scale

CO_2 laser vs. PRP

Critical outcomes

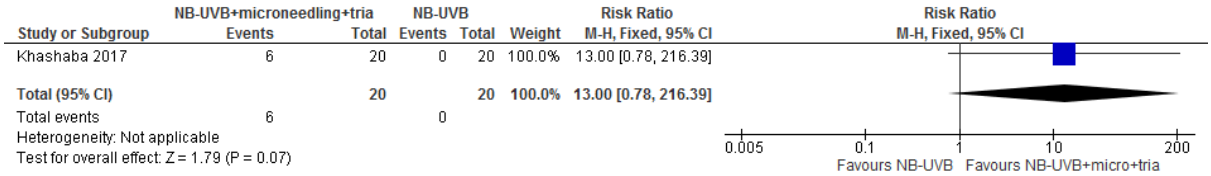
- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up



NB-UVB + micro-needling + topical triamcinolone vs. NB-UVB

Critical outcomes

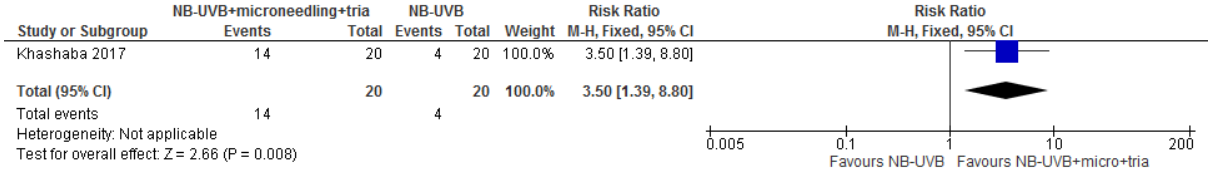
- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up



N.B. Change in scale

<u>Important outcomes</u>

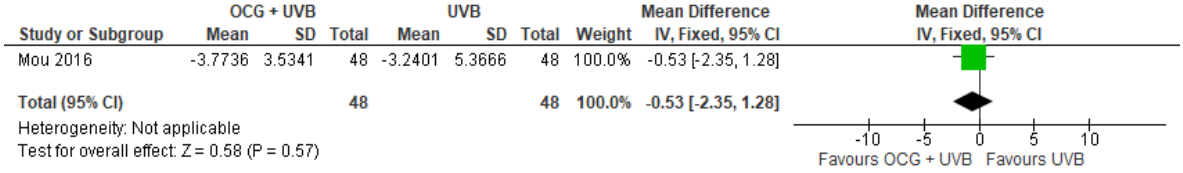
- Repigmentation ≥50% (>50%) in **patients** at 5-month follow-up



Oral compound glycyrrhizin (OCG) + NB-UVB vs. NB-UVB

<u>Critical outcomes</u>

- Change in QoL (DLQI) in **patients** at 6-month follow-up

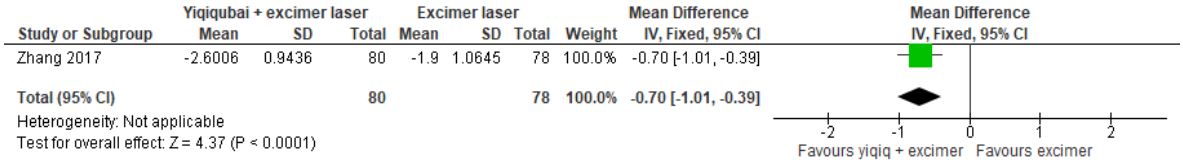


N.B. Change in scale

Yiqiqubai granules + excimer laser vs. excimer laser

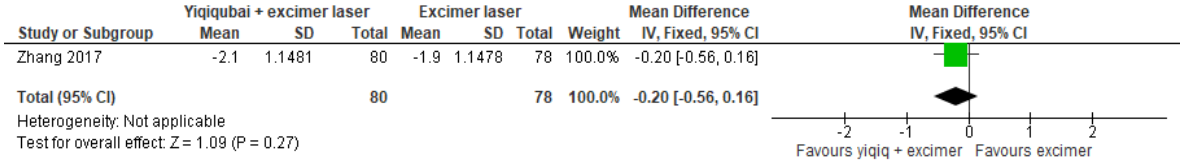
<u>Critical outcomes</u>

- Change in QoL (Embarrassment) in **patients** at 6-month follow-up

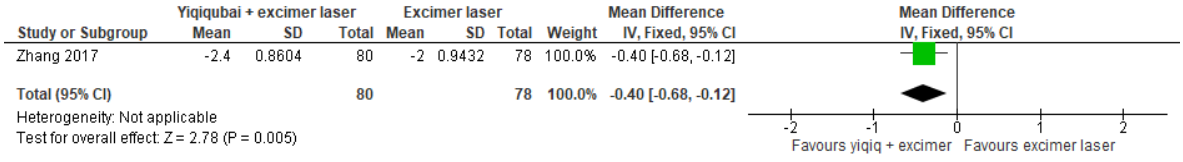


N.B. Change in scale

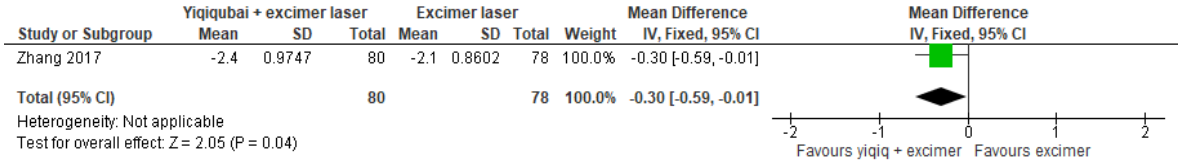
- Change in QoL (Dress) in **patients** at 6-month follow-up



- Change in QoL (Social) in **patients** at 6-month follow-up

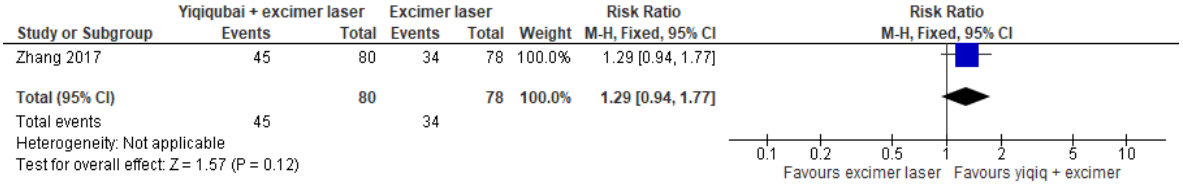


- Change in QoL (Work) in **patients** at 6-month follow-up



Important outcomes

- Repigmentation ≥50% in **patients** at 6-month follow-up

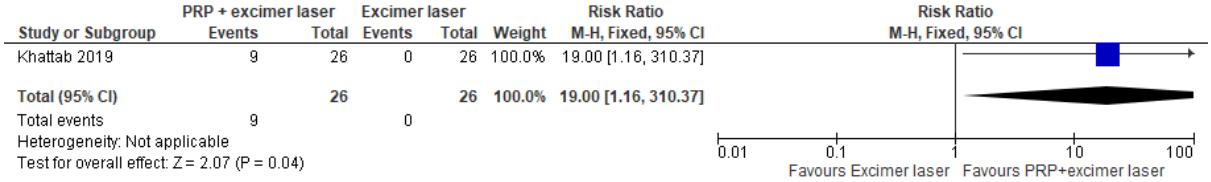


N.B. Change in scale

PRP + excimer laser vs. excimer laser

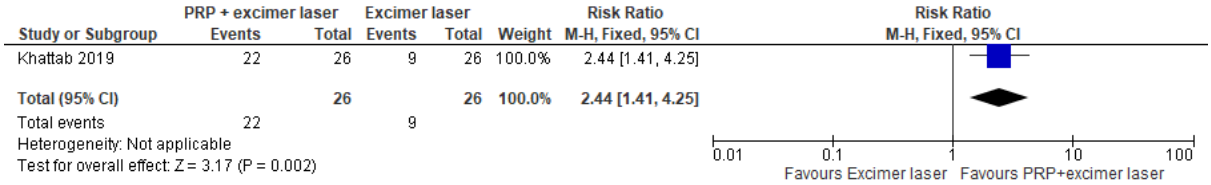
Critical outcomes

- Repigmentation ≥ 75% in **patients** at 3-month post-treatment follow-up



Important outcomes

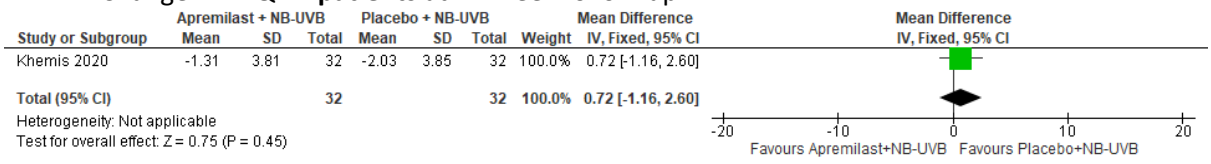
- Repigmentation ≥ 50% in **patients** at 3-month post-treatment follow-up



Apremilast + NB-UVB vs. placebo + NB-UVB

Critical outcomes

- Change in DLQI in **patients** at 24-week follow-up

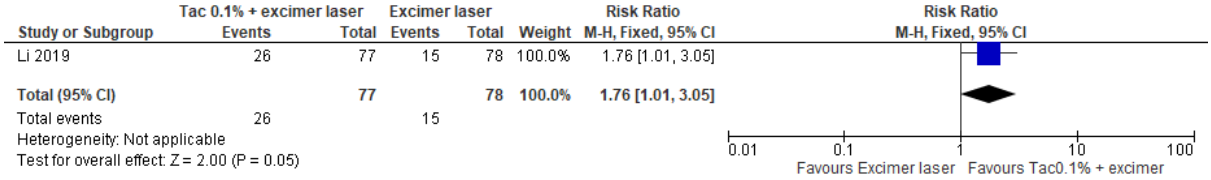


N.B. Change in scale

Tacrolimus 0.1% + excimer laser vs. excimer laser

Critical outcomes

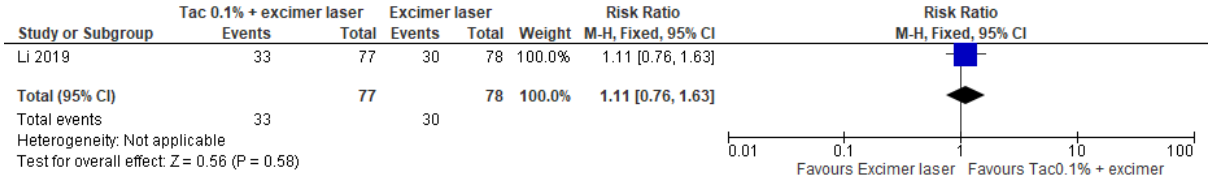
- Complete repigmentation in **lesions** at 12-week follow-up



N.B. Change in scale

Important outcomes

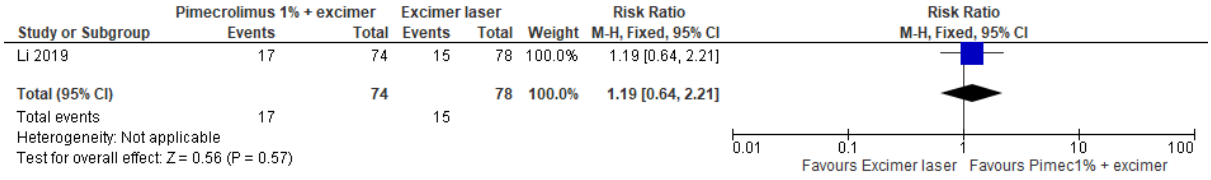
- Repigmentation ≥ 50% (>50%) in **lesions** at 12-week follow-up



Pimecrolimus 1% + excimer laser vs. excimer laser

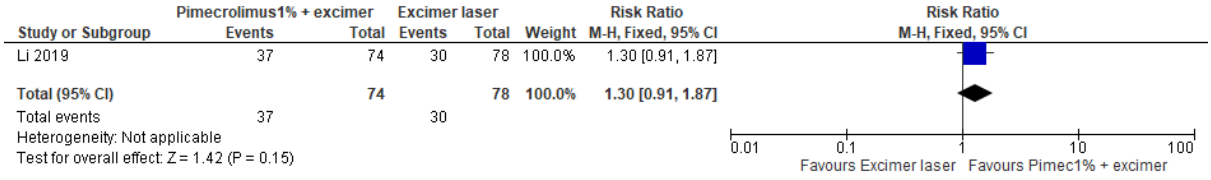
Critical outcomes

- Complete repigmentation in **lesions** at 12-week follow-up



Important outcomes

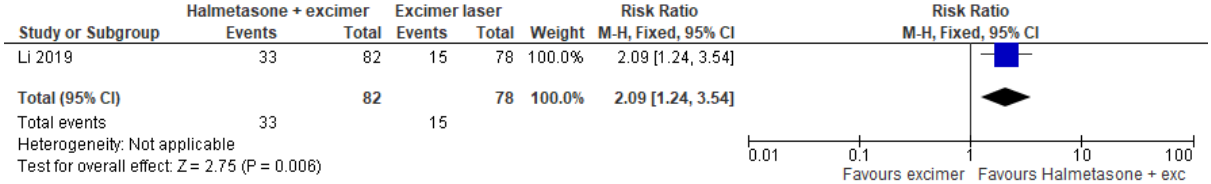
- Repigmentation ≥ 50% (>50%) in **lesions** at 12-week follow-up



Halometasone + excimer laser vs. excimer laser

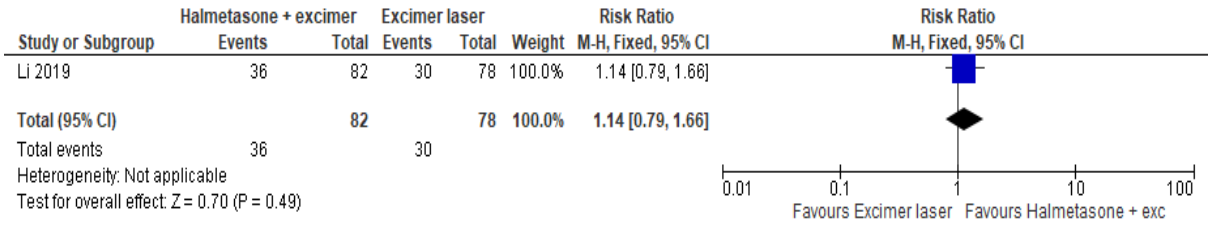
Critical outcomes

- Complete repigmentation in **lesions** at 12-week follow-up



Important outcomes

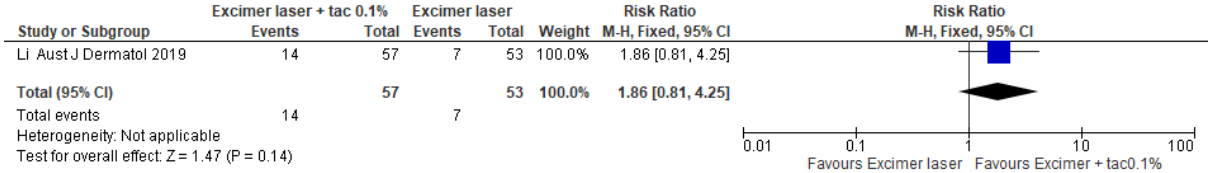
- Repigmentation ≥ 50% (>50%) in **lesions** at 12-week follow-up



Excimer laser + tacrolimus 0.1% vs. excimer laser

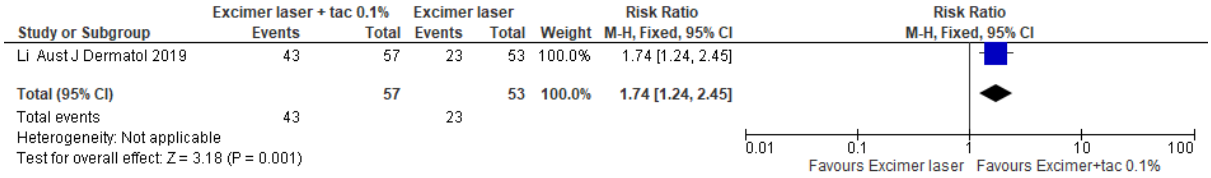
Critical outcomes

- Complete repigmentation in **lesions** at 12-week follow-up



Important outcomes

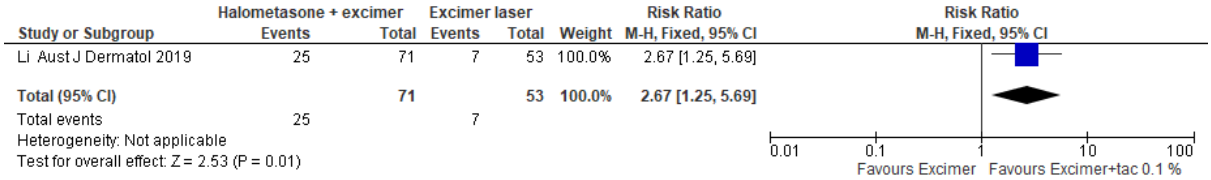
- Repigmentation ≥ 50% (>50%) in **lesions** at 12-week follow-up



Halometasone + excimer laser vs. excimer laser

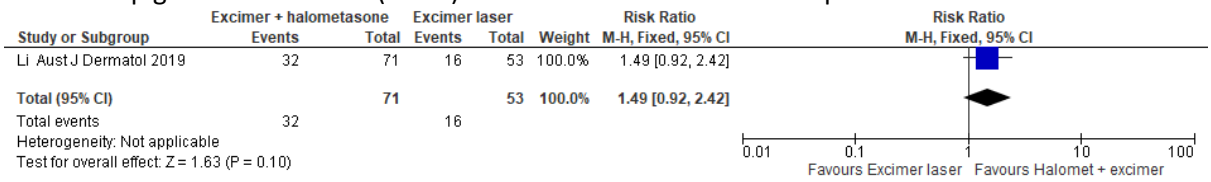
Critical outcomes

- Complete repigmentation in **lesions** at 12-week follow-up



Important outcomes

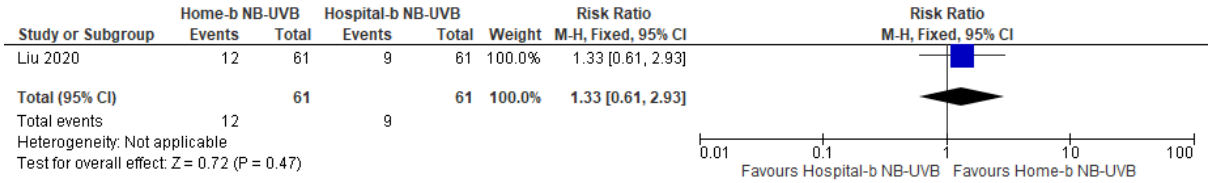
- Repigmentation ≥ 50% (>50%) in **lesions** at 12-week follow-up



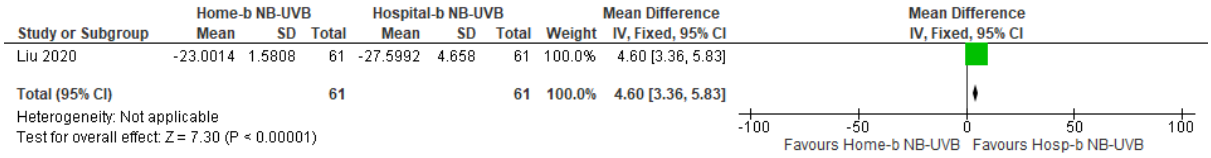
Home-based NB-UVB (Home-b NB-UVB) vs. Hospital-based NB-UVB (Hosp-b NB-UVB)

Critical outcomes

- Repigmentation ≥ 75% (>75%) in **patients** at 3-month follow-up

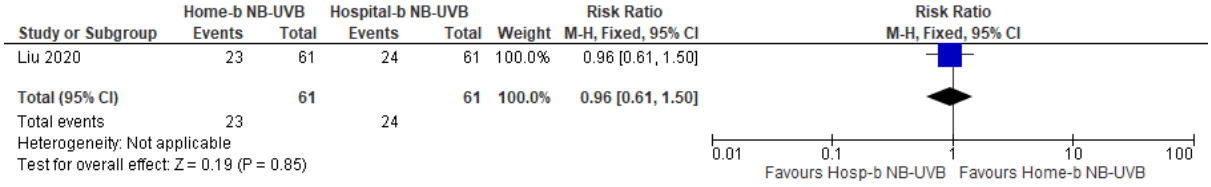


- Change in VitiQoL scores in **patients** at 20-week follow-up



Important outcomes

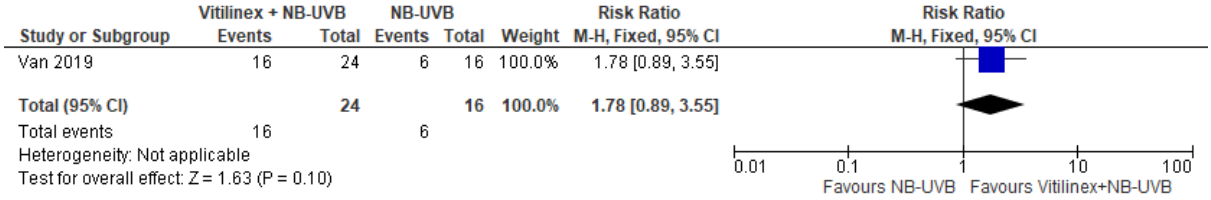
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



Vitilinex + NB-UVB vs. NB-UVB

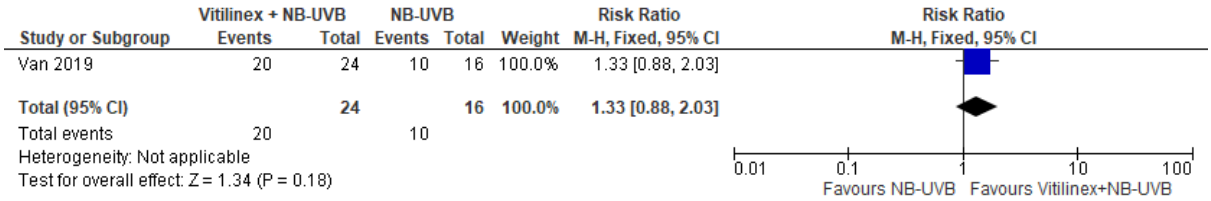
Critical outcomes

- Repigmentation ≥ 75% (>75%) in **patients** at 12-week follow-up



Important outcomes

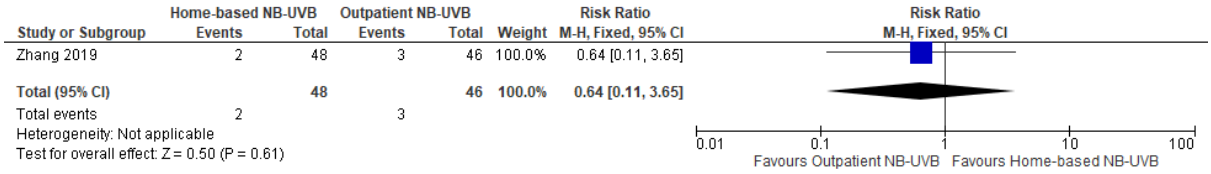
- Repigmentation ≥ 50% (>50%) in **patients** at 12-week follow-up



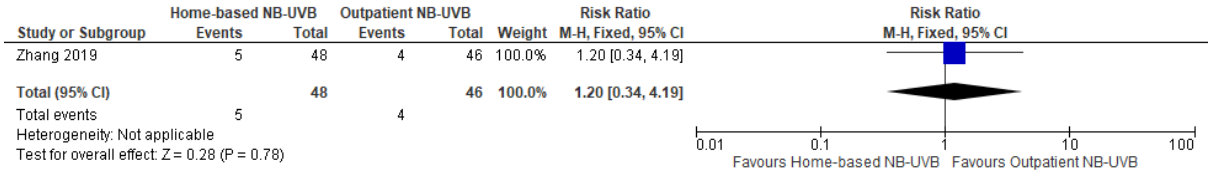
Home-based NB-UVB vs. outpatient NB-UVB

Critical outcomes

- Repigmentation ≥ 75% in **patients** at 6-month follow-up

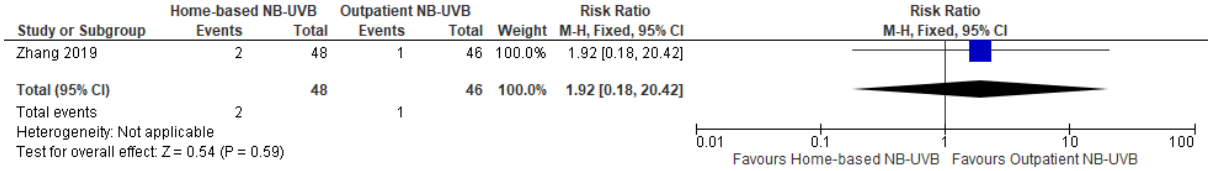


- Painful erythema in **patients** at 6-month follow-up

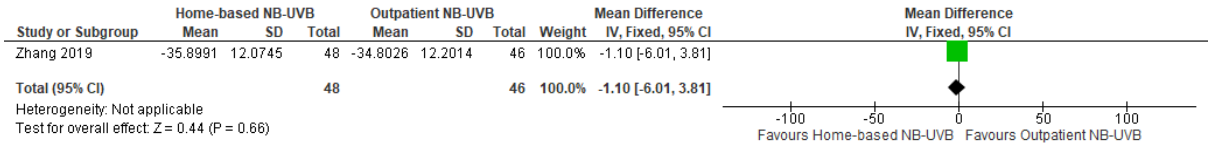


- Pruritus in **patients** at 6-month follow-up

- Skin-burning in **patients** at 6-month follow-up

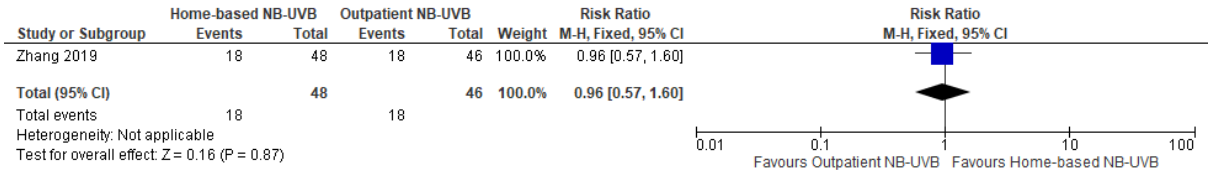


- Change in QoL (vitiQoL) in **patients** at 6-month follow-up



<u>Important outcomes</u>

- Repigmentation ≥ 50% in **patients** at 6-month follow-up

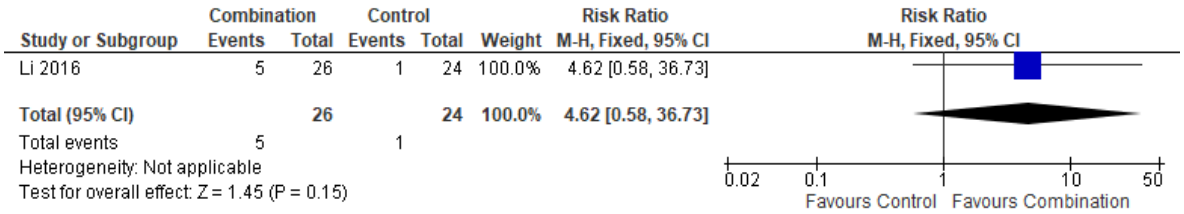


Combination Therapies

Alpha lipoic acid + betamethasone injection + NB-UVB (combination) vs. placebo + betamethasone injection + NB-UVB (control)

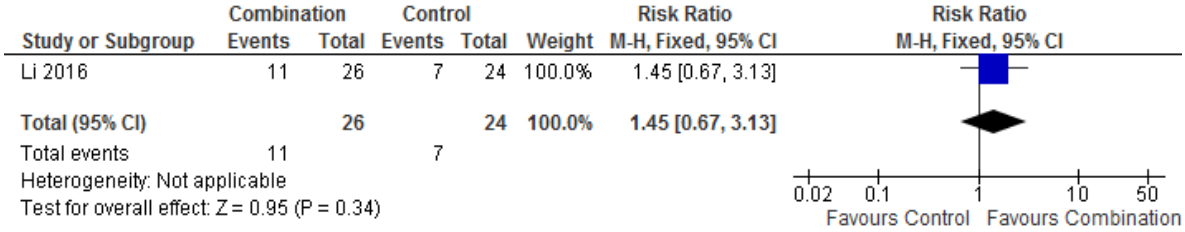
<u>Critical outcomes</u>

- Repigmentation ≥75% (>75%) in **patients** at 3-month follow-up



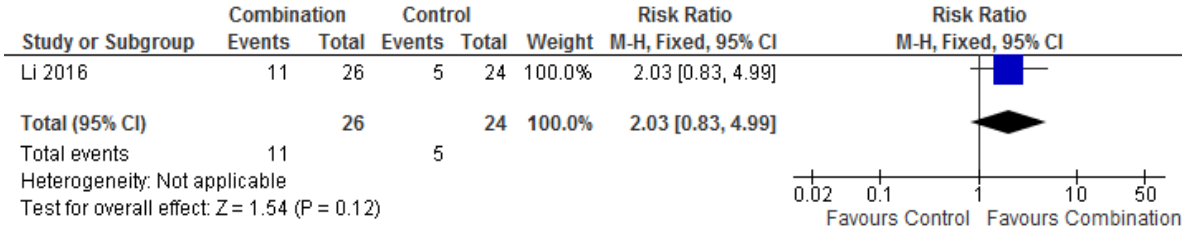
N.B. Change in scale

- Repigmentation ≥75% (>75%) in **patients** at 6-month follow-up

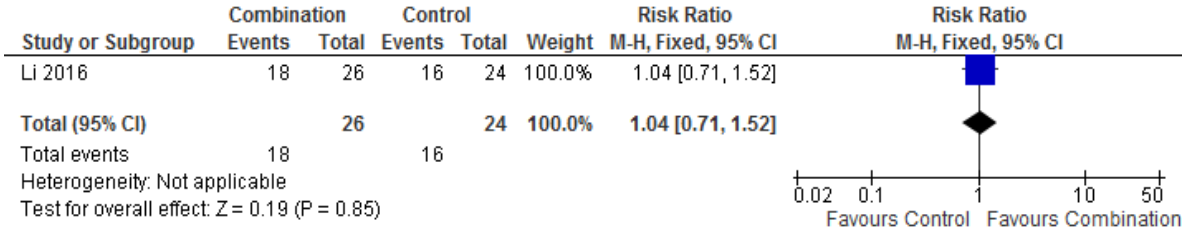


<u>Important outcomes</u>

- Repigmentation ≥50% (>50%) in **patients** at 3-month follow-up



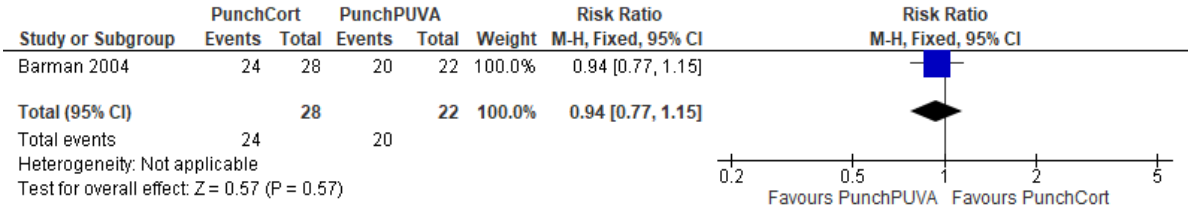
- Repigmentation ≥50% (>50%) in **patients** at 6-month follow-up



Punch grafting + corticosteroids vs. punch grafting + PUVA

<u>Important outcomes</u>

- Cosmetically acceptability in **patients** at 6-month follow-up

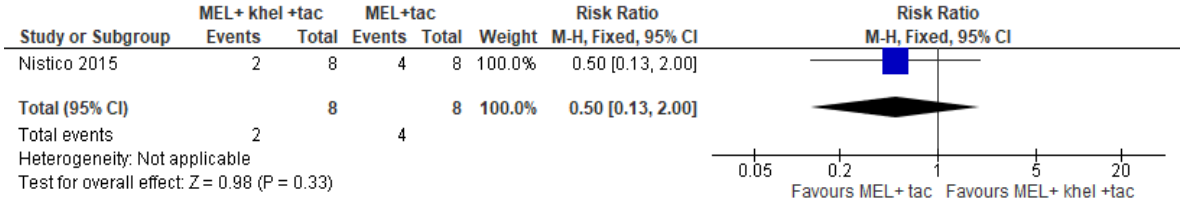


N.B. Change in scale

MEL + khellin + tacrolimus vs. MEL + tacrolimus

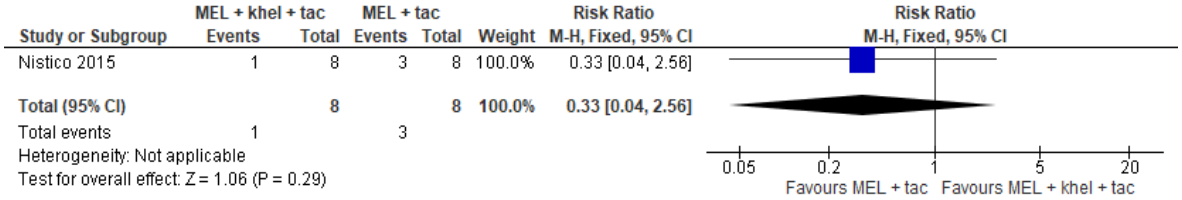
<u>Critical outcomes</u>

- Repigmentation ≥75% (>75%) in **patients** at 3-month follow-up



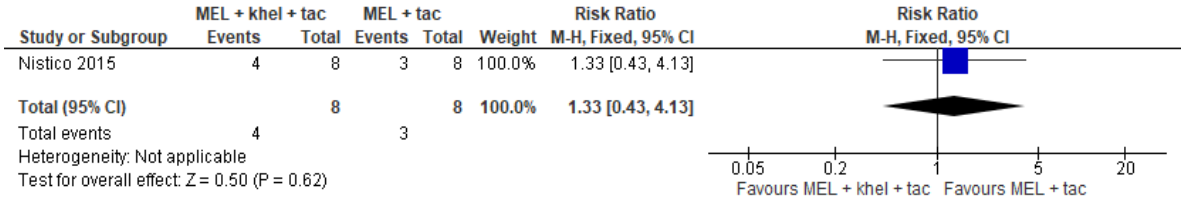
N.B. Change in scale

N.B. Complete repigmentation (100%) in **patients** at 3-month follow-up

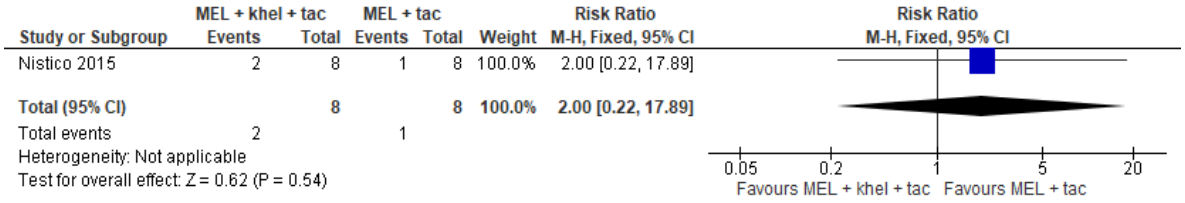


N.B. Change in scale

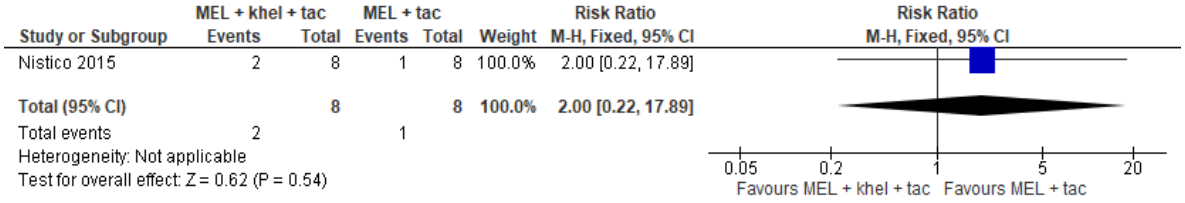
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

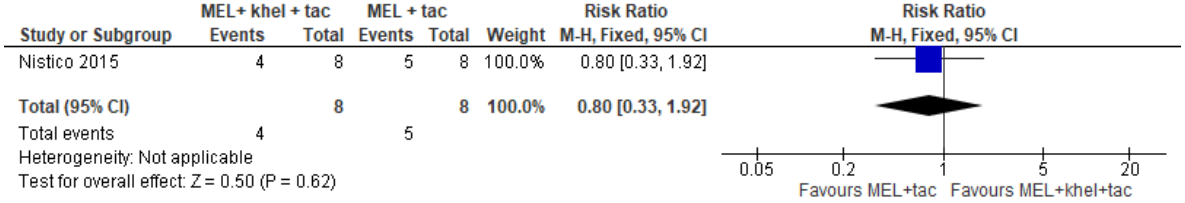


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



<u>Important outcomes</u>

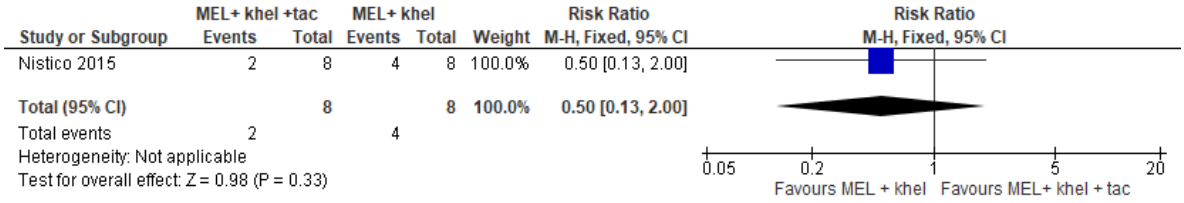
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



MEL + khellin + tacrolimus vs. MEL + khellin

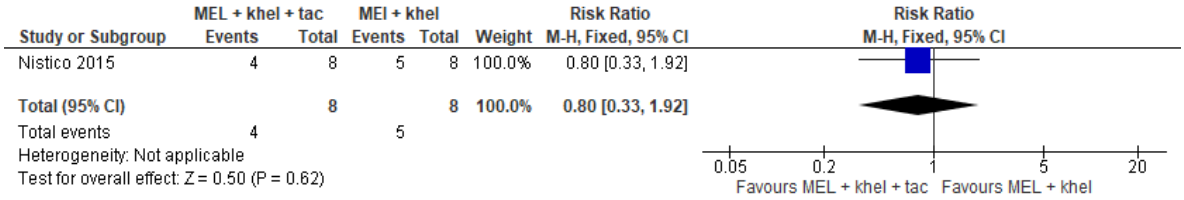
Critical outcomes

- Repigmentation ≥ 75% (>75%) in **patients** at 3-month follow-up

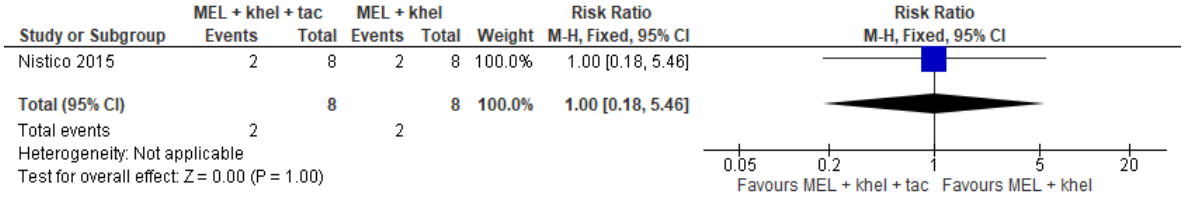


N.B. Complete repigmentation (100%) in **patients** at 3-month follow-up

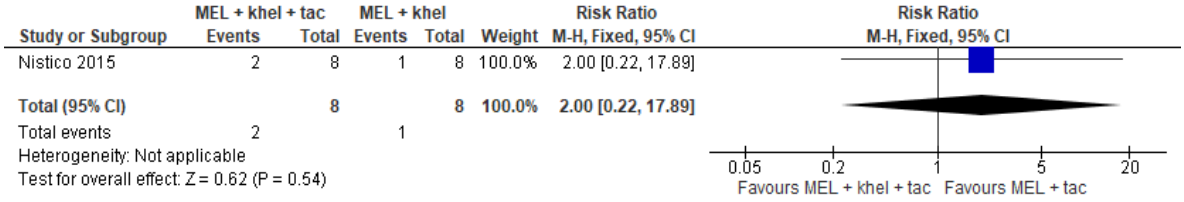
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

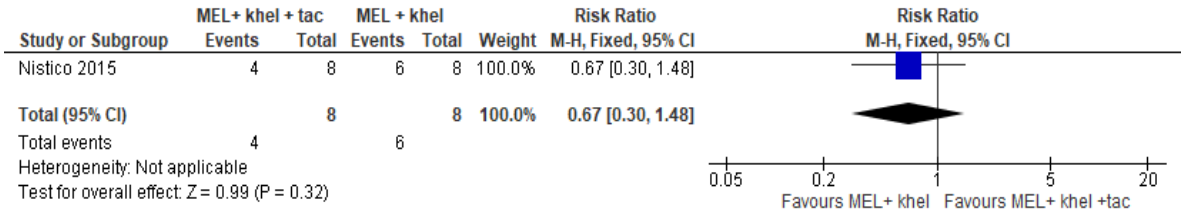


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



Important outcomes

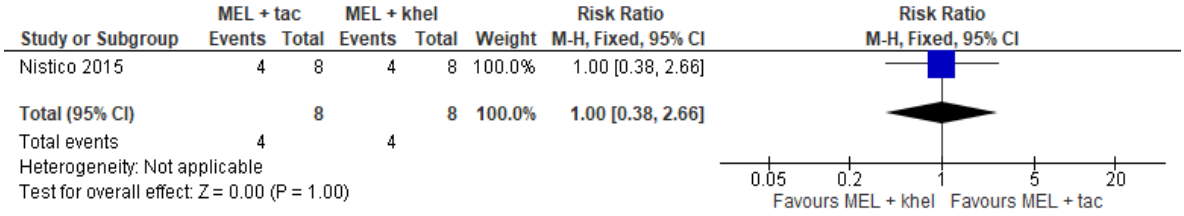
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



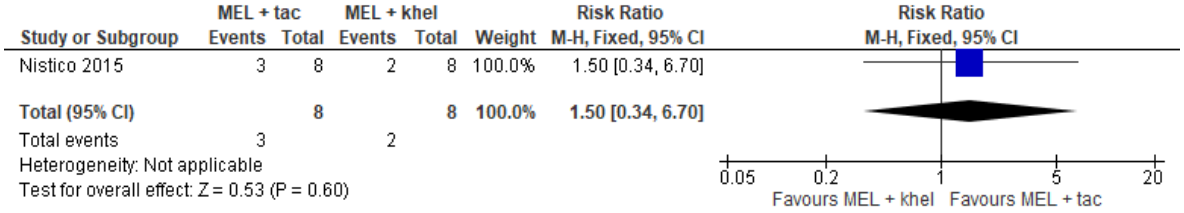
MEL + tacrolimus vs. MEL + khellin

<u>Critical outcomes</u>

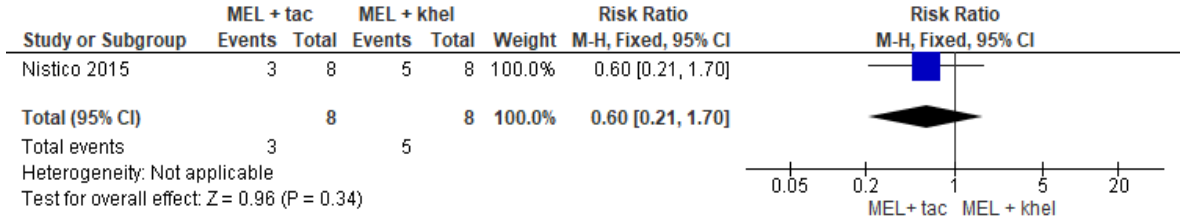
- Repigmentation ≥ 75% (>75%) in **patients** at 3-month follow-up



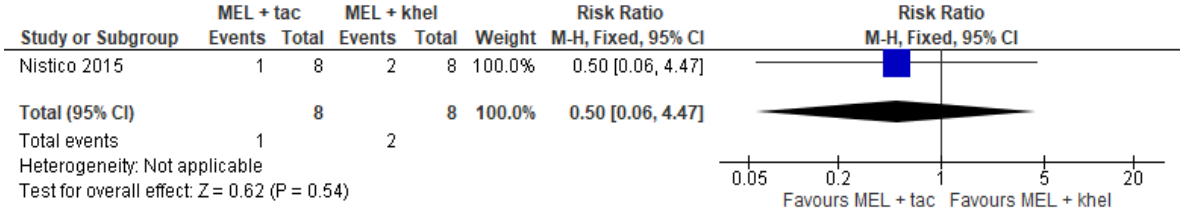
N.B. Complete repigmentation (100%) in **patients** at 3-month follow-up



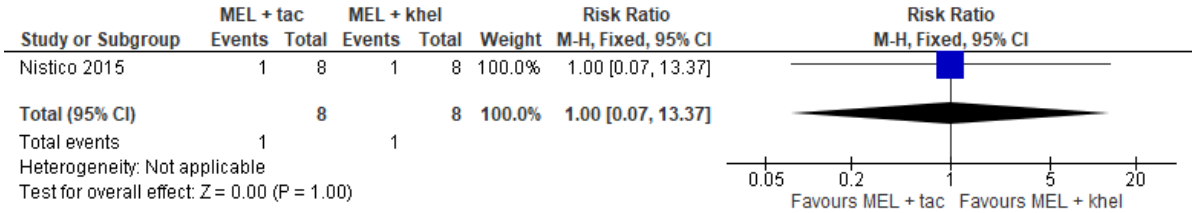
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

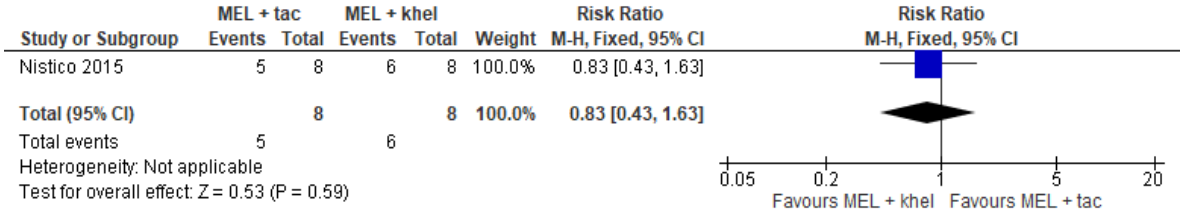


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



Important outcomes

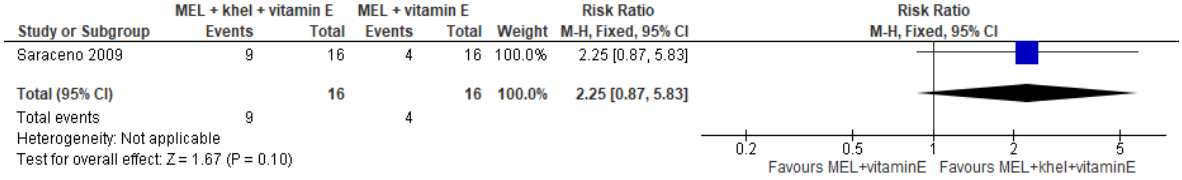
- Repigmentation ≥ 50% (>50%) in **patients** at 3-month follow-up



MEL + khel + oral vitamin E vs. MEL + oral vitamin E

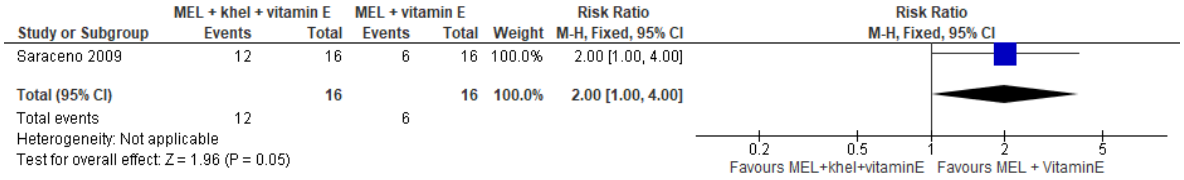
Critical outcomes

- Repigmentation ≥ 75% (>75%) in **patients** at 12 wks. follow-up

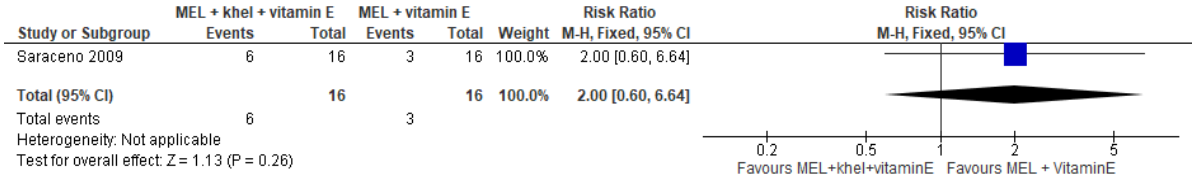


N.B. Change in scale

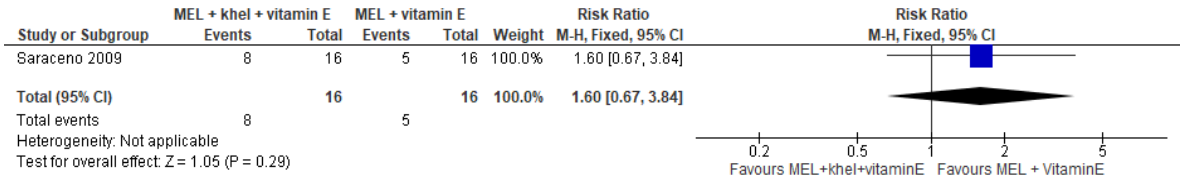
- Erythema in **patients** at 3-month follow-up



- Burning-pain in **patients** at 3-month follow-up

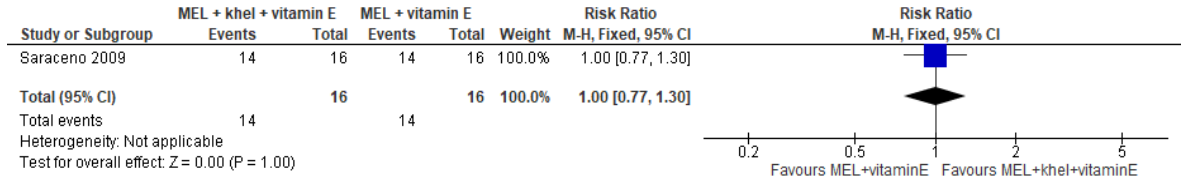


- Perilesional hyperpigmentation in **patients** at 3-month follow-up



Important outcomes

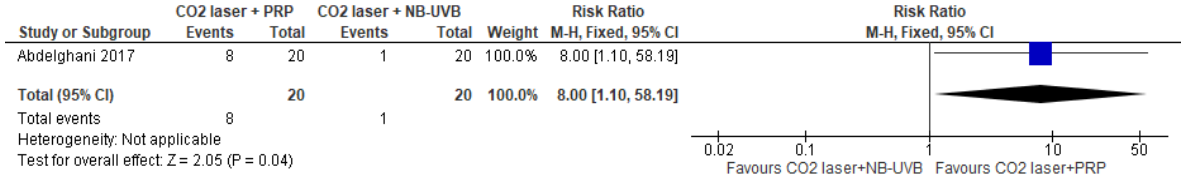
- Repigmentation ≥ 50% (>50%) in **patients** at 12 wks. follow-up



CO_2 laser + PRP vs. CO_2 laser + NB-UVB

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up

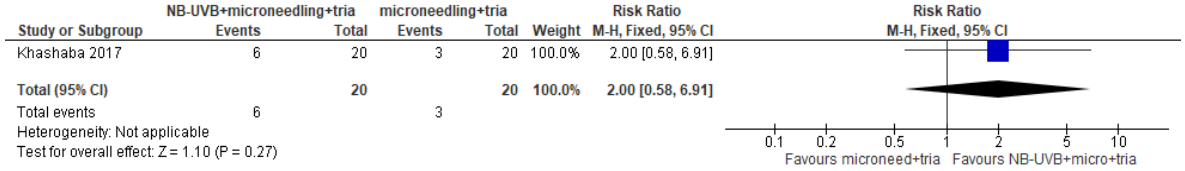


N.B. Change in scale

NB-UVB + micro-needling + topical triamcinolone vs. micro-needling + topical triamcinolone

Critical outcomes

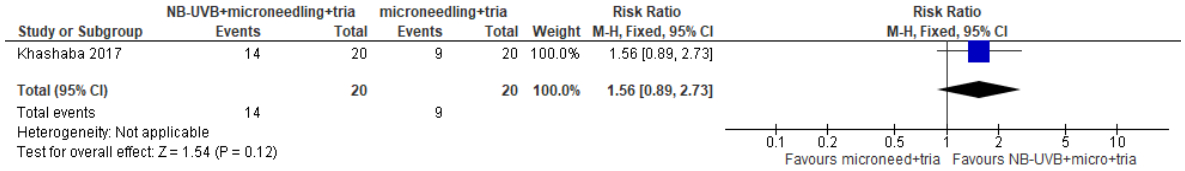
- Repigmentation ≥75% (>75%) in **patients** at 3-month follow-up



N.B. Change in scale

Important outcomes

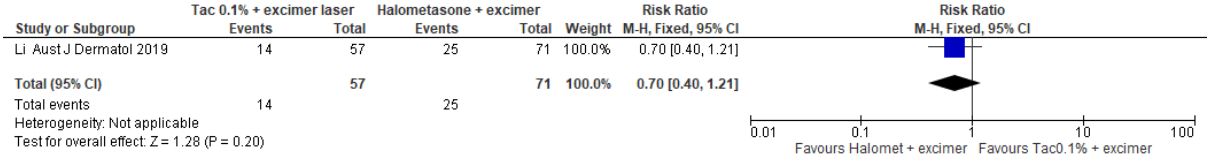
- Repigmentation ≥50% (>50%) in **patients** at 3-month follow-up



Tacrolimus 0.1% + excimer laser vs. Halometasone + excimer laser

Critical outcomes

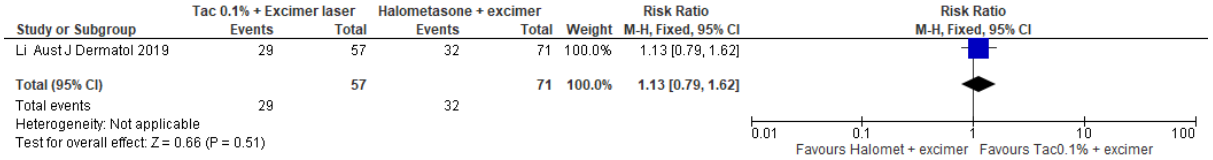
- Complete repigmentation in **lesions** at 12-week follow-up



N.B. Change in scale

Important outcomes

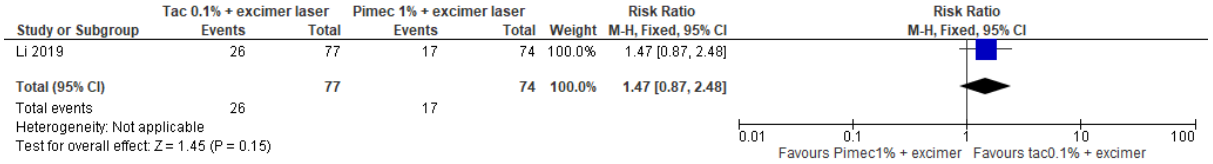
- Repigmentation > 50% (≥ 50%) in **lesions** at 12-week follow-up



Tacrolimus 0.1% + excimer laser vs. pimecrolimus 1% + excimer laser

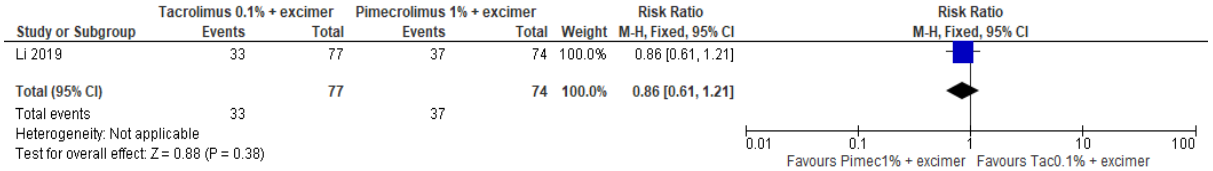
Critical outcomes

- Complete repigmentation in **lesions** at 12-week follow-up



Important outcomes

- Repigmentation > 50% (≥ 50%) in **lesions** at 12-week follow-up



Tacrolimus 0.1% + excimer laser vs. Halometasone + excimer laser

Critical outcomes

- Complete repigmentation in **lesions** at 12-week follow-up

Important outcomes

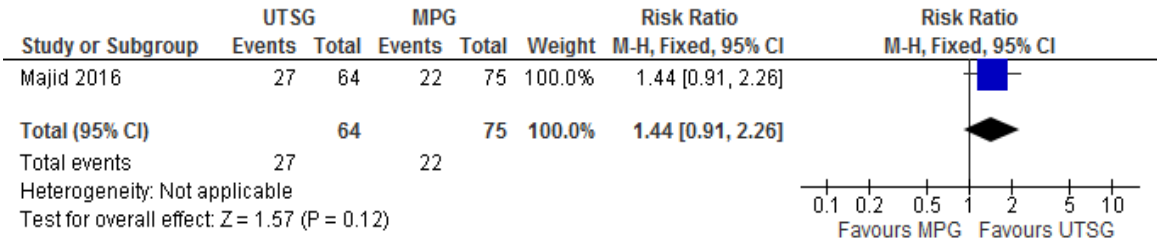
- Repigmentation ≥ 50% (> 50%) in **lesions** at 12-week follow-up

Surgical Therapies

Ultra-thin skin grafting (UTSG) vs. miniature punch grafting (MPG)

Critical outcomes

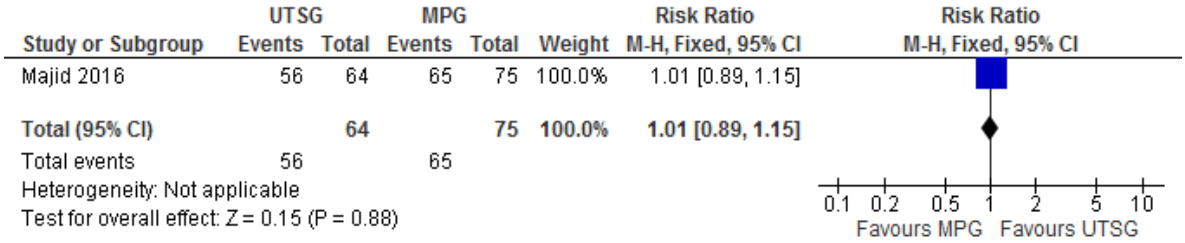
- Repigmentation ≥ 75% (N.B. ≥90%) in **lesions** at 6-month follow-up



N.B. Change in scale

Important outcomes

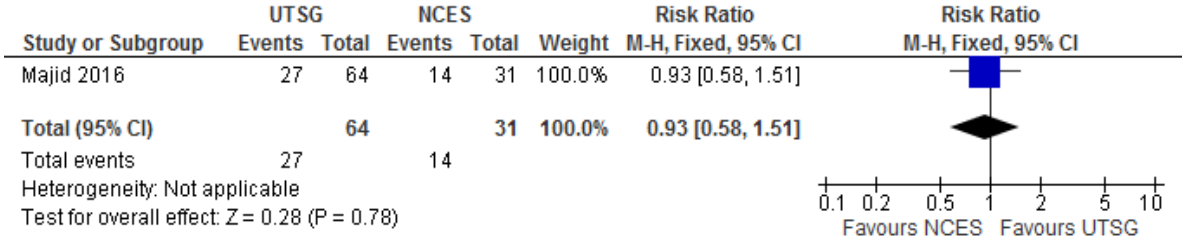
- Repigmentation (≥50%) in **lesions** at 6-month follow-up



Ultra-thin skin grafting (UTSG) vs. Nocturnal epidermal cell suspension (NCES)

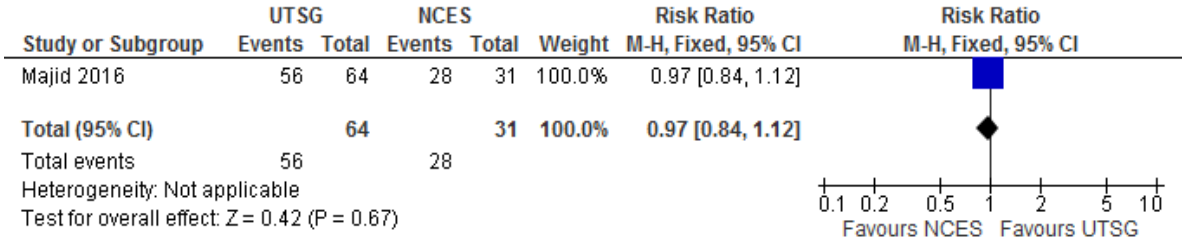
Critical outcomes

- Repigmentation ≥ 75% (N.B. ≥90%) in **lesions** at 6-month follow-up



Important outcomes

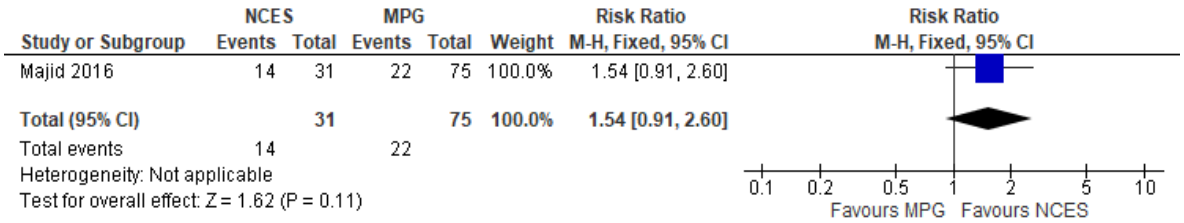
- Repigmentation (≥50%) in **lesions** at 6-month follow-up



NCES vs. miniature punch grafting (MPG)

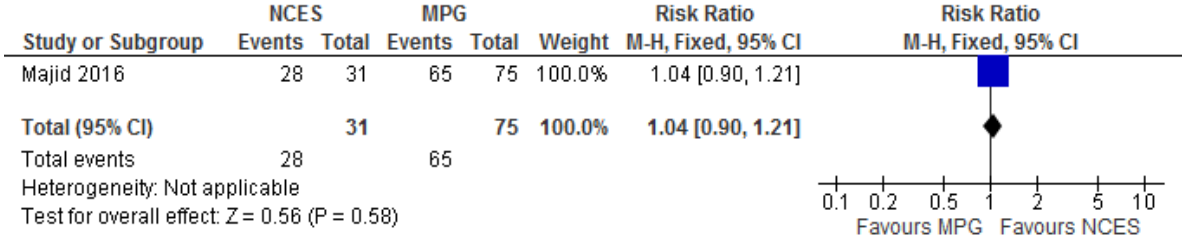
Critical outcomes

- Repigmentation ≥ 75% (N.B. ≥90%) in **lesions** at 6-month follow-up



Important outcomes

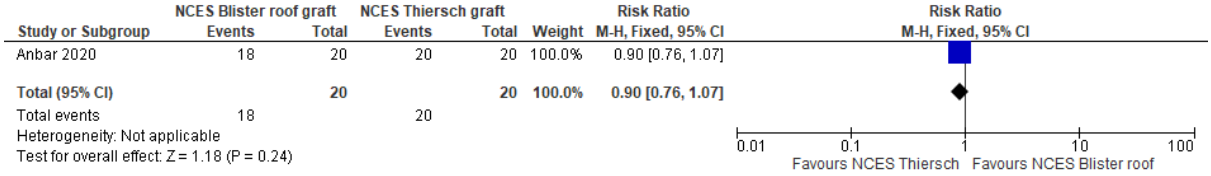
- Repigmentation (≥50%) in **lesions** at 6-month follow-up



NCES Blister roof graft vs. NCES partial thickness epidermal cuts (Thiersch graft)

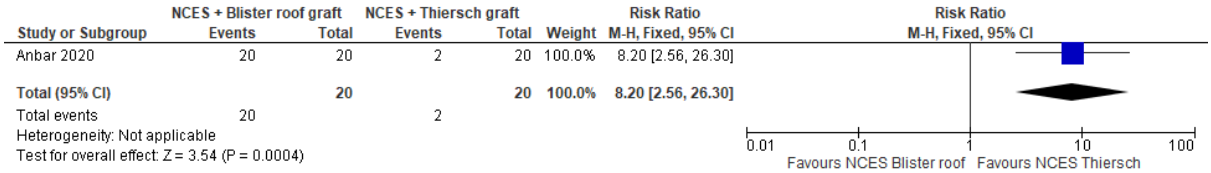
Critical outcomes

- Repigmentation ≥ 75% in **patients** at 3-month post-treatment follow-up



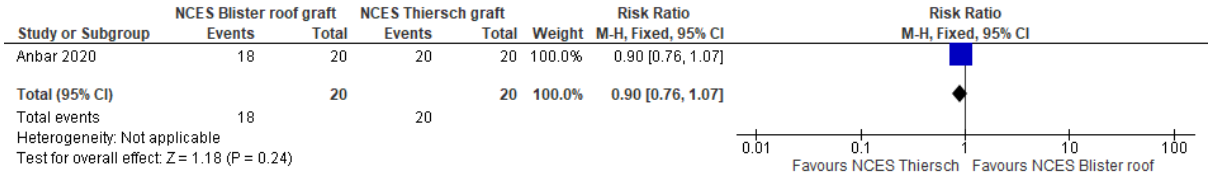
N.B. Change in scale

- Hyperpigmentation in **patients** at 3-month post-treatment follow-up



Important outcomes

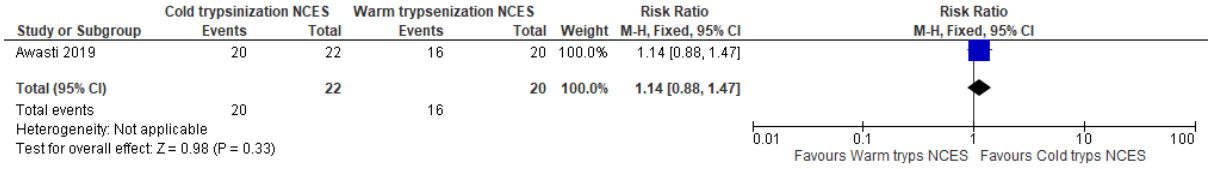
- Repigmentation ≥ 50% in **patients** at 3-month post-treatment follow-up



Cold trypsinization preparation vs. warm trypsinization preparation NCES

Critical outcomes

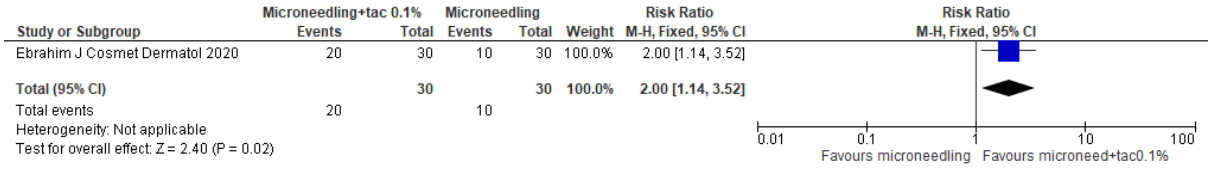
- Repigmentation ≥75% in **lesions** at 16-week follow-up



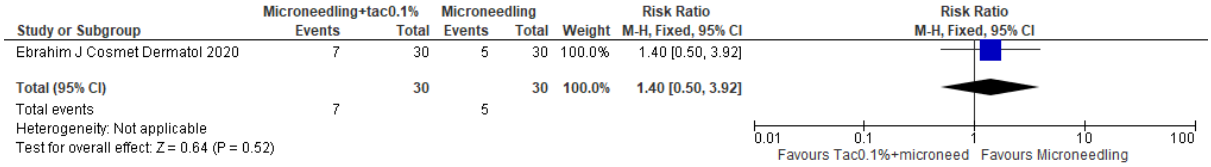
Tacrolimus 0.1% + microneedling vs. microneedling

Critical outcomes

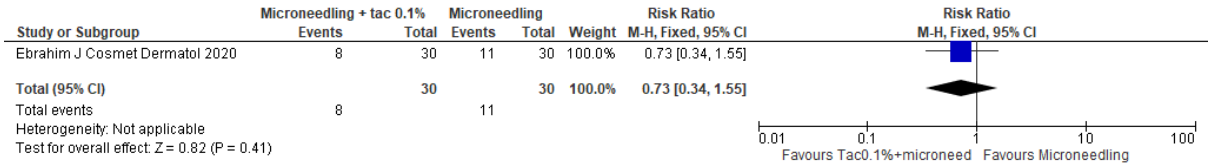
- Repigmentation ≥ 75% in **patients** at 3-month post-treatment follow-up



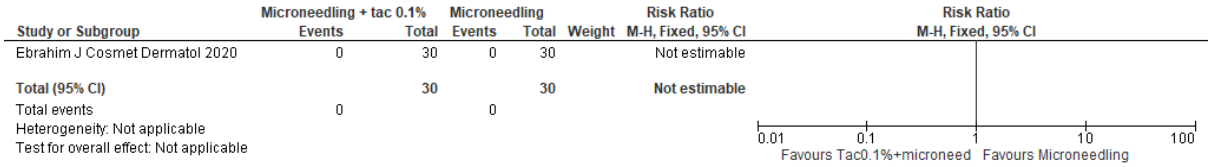
- Erythema in **patients** at 3-month post-treatment follow-up



- Pain in **patients** at 3-month post-treatment follow-up

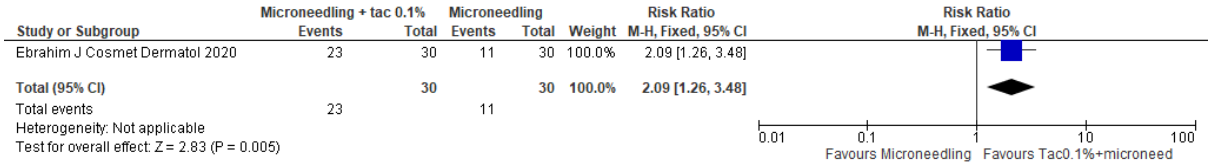


- Itching in **patients** at 3-month post-treatment follow-up



Important outcomes

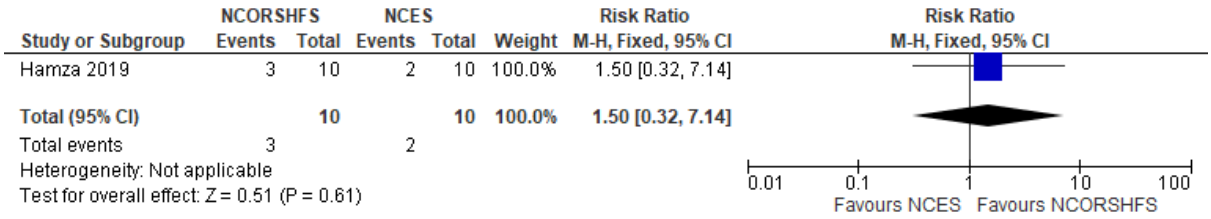
- Repigmentation ≥ 50% in **patients** at 3-month post-treatment follow-up



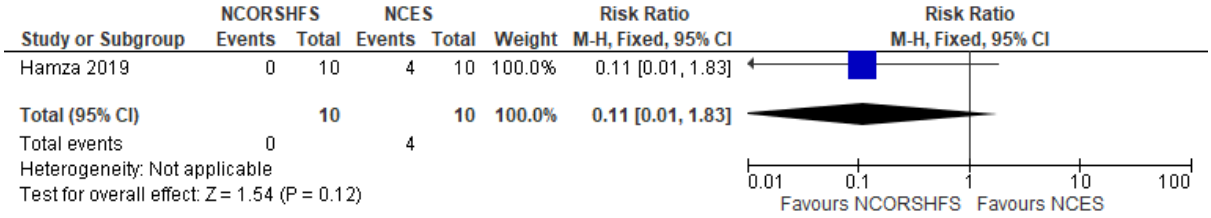
Non-cultured extracted hair follicle outer root sheath (NCORSHFS) vs. NCES

Critical outcomes

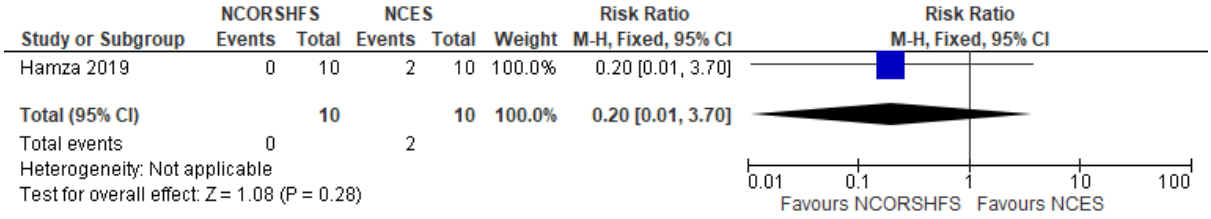
- Repigmentation ≥ 75% in **patients** at 3-month follow-up, NCORSHFS vs. NCES



- Hyperpigmentation in **patients** at 3-month follow-up, NCORSHFS vs. NCES

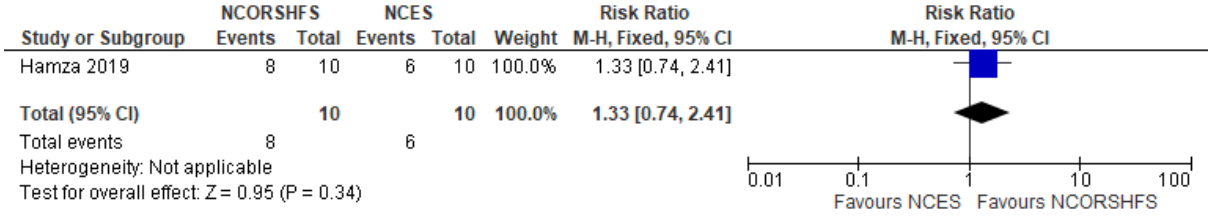


- Mild scarring in **patients** at 3-month follow-up, NCORSHFS vs. NCES



Important outcomes

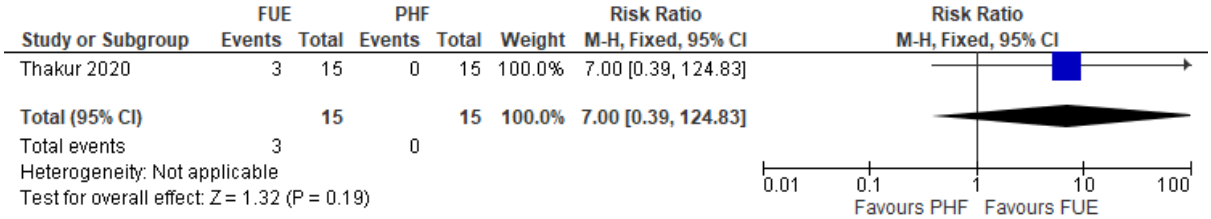
- Repigmentation ≥ 50% in **patients** at 3-month follow-up, NCORSHFS vs. NCES



Follicular unit extraction (FUE) vs. plucking hair follicles (PHF)

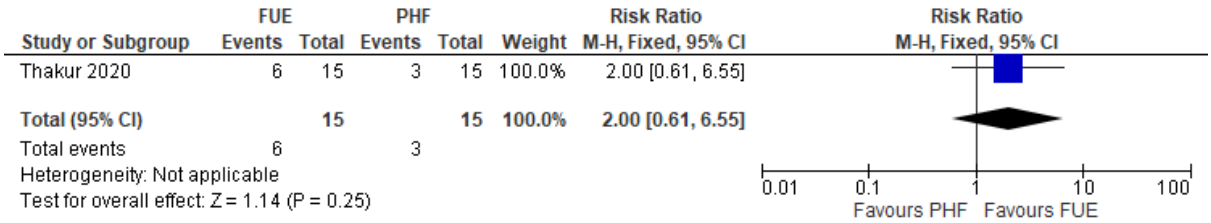
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 16-week post-treatment follow-up



Important outcomes

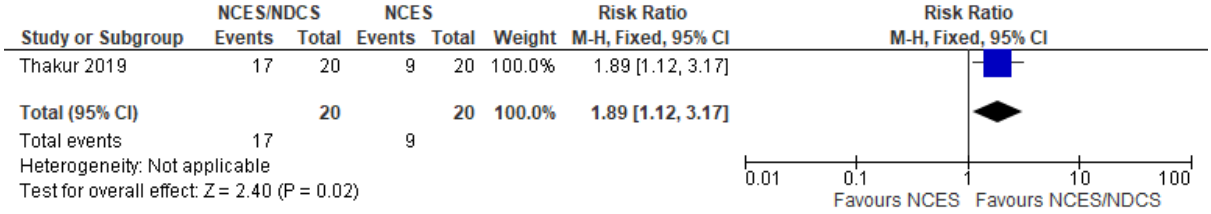
- Repigmentation ≥ 50% (>50%) in **patients** at 16-week post-treatment follow-up



NCES/ non-cultured dermal cell suspension (NDCS) vs. NCES

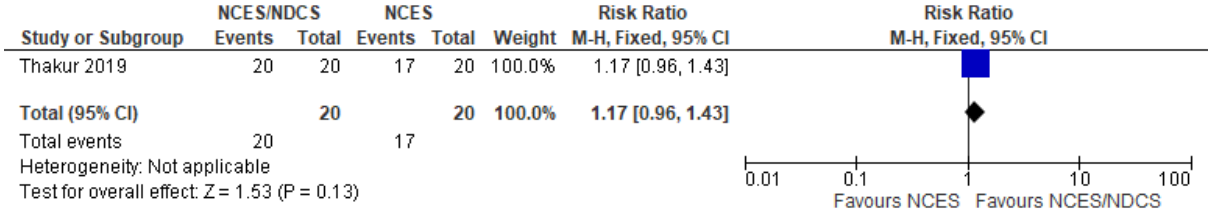
Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 24-week post-treatment follow-up



Important outcomes

- Repigmentation ≥50% (>50%) in **patients** at 24-week post-treatment follow-up

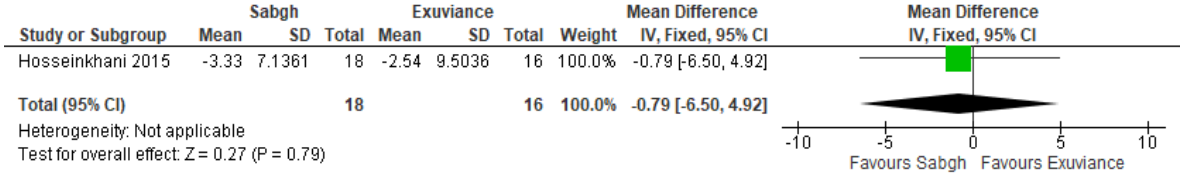


Skin camouflage Therapies

Sabgh (herbal formulation) vs. Exuviance (active ingredient is titanium dioxide)

Critical outcomes

- QoL (DLQI) in **patients** at 8-week follow-up



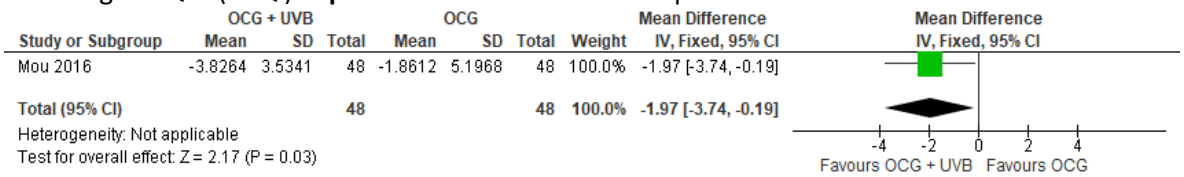
N.B. Change in scale

Complementary Therapies

OCG + NB-UVB vs. OCG

Critical outcomes

- Change in QoL (DLQI) in **patients** at 6-month follow-up

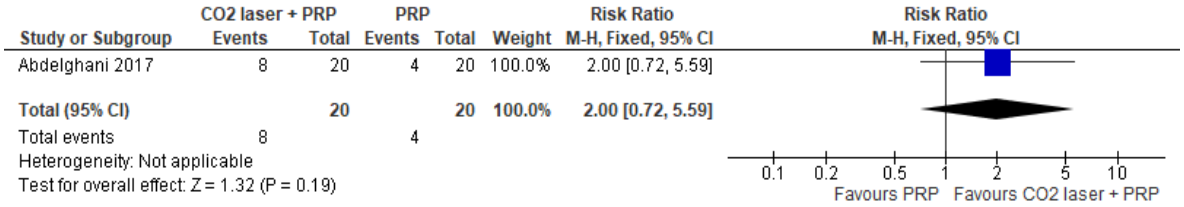


N.B. Change in scale

CO_2 laser + PRP vs. PRP

Critical outcomes

- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up

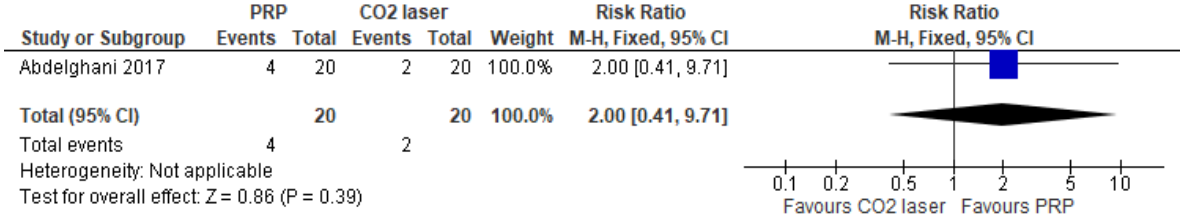


N.B. Change in scale

PRP vs. CO_2

Critical outcomes

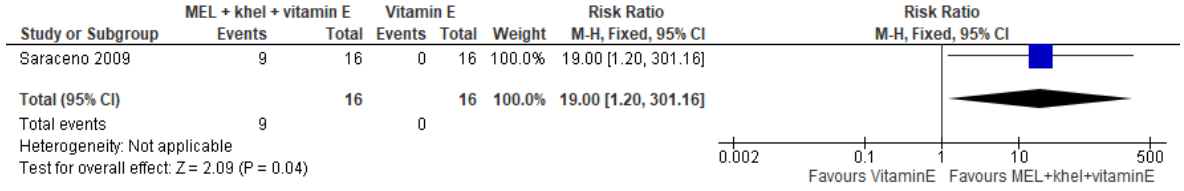
- Repigmentation ≥75% (>75%) in **patients** at 5-month follow-up



MEL + khel + oral vitamin E vs. oral vitamin E

Critical outcomes

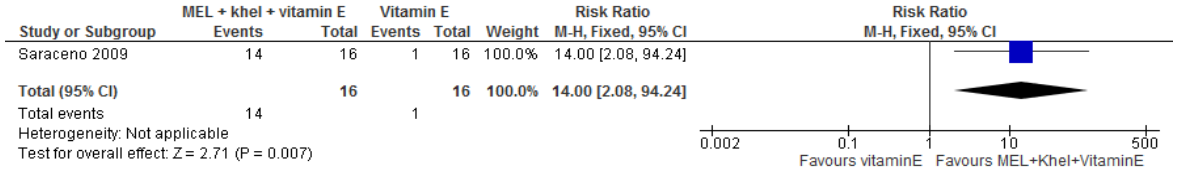
- Repigmentation ≥ 75% (>75%) in **patients** at 12 wks. follow-up



N.B. Change in scale

Important outcomes

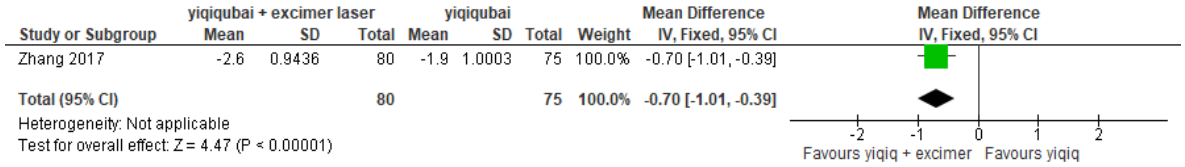
- Repigmentation ≥ 50% (>50%) in **patients** at 12 wks. follow-up



Yiqiqubai granules + excimer laser vs. yiqiqubai granules

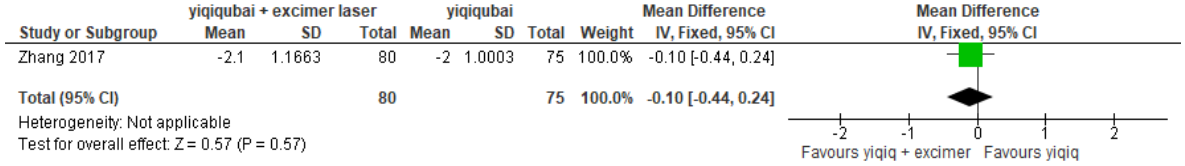
Critical outcomes

- Change in QoL (Embarrassment) in **patients** at 6-month follow-up

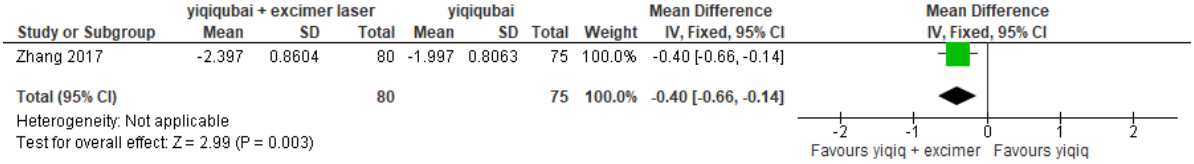


N.B. Change in scale

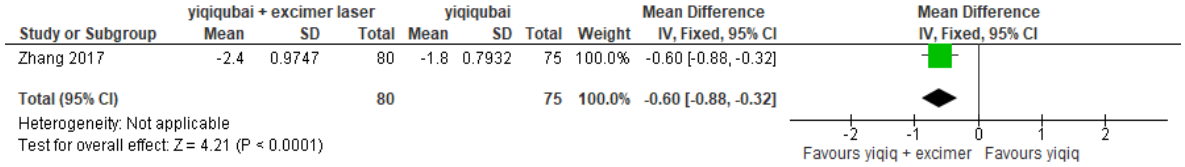
- Change in QoL (Dress) in **patients** at 6-month follow-up



- Change in QoL (Social) in **patients** at 6-month follow-up

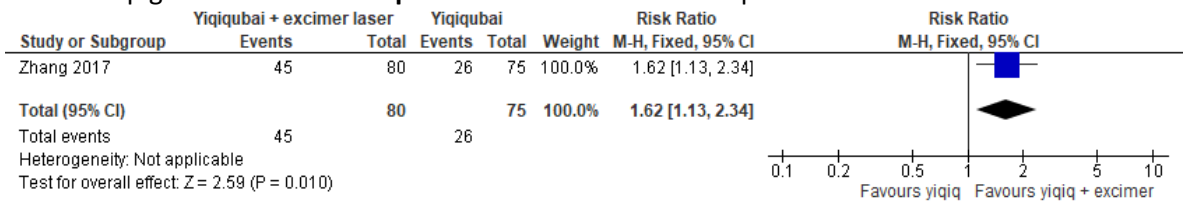


- Change in QoL (Work) in **patients** at 6-month follow-up



<u>Important outcomes</u>

- Repigmentation ≥50% in **patients** at 6-month follow-up

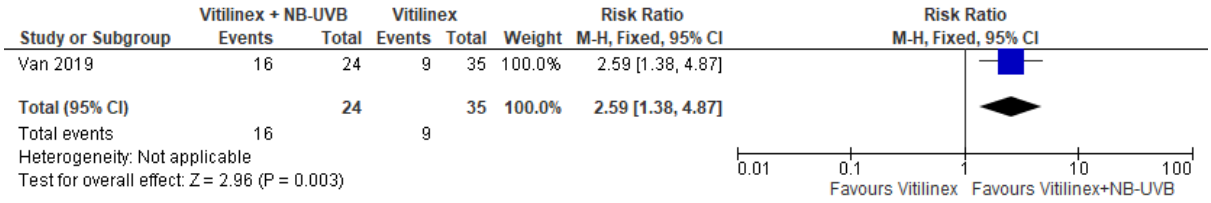


N.B. Change in scale

Vitilinex (herbal bio-actives) + NB-UVB vs. Vitilinex (herbal bioactives)

<u>Critical outcomes</u>

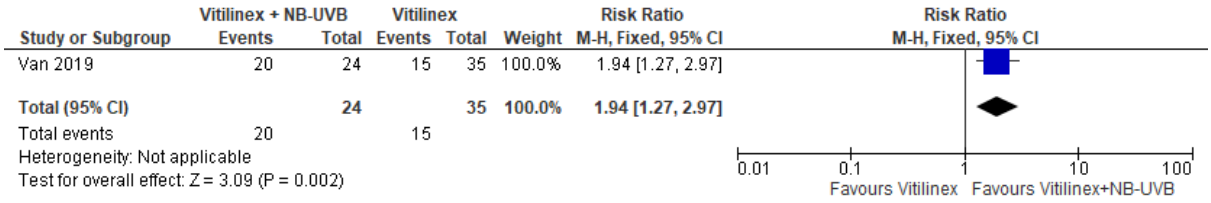
- Repigmentation ≥ 75% (>75%) in **patients** at 12-week follow-up



N.B. Change in scale

Important outcomes

- Repigmentation ≥ 50% (> 50%) in **patients** at 12-week follow-up

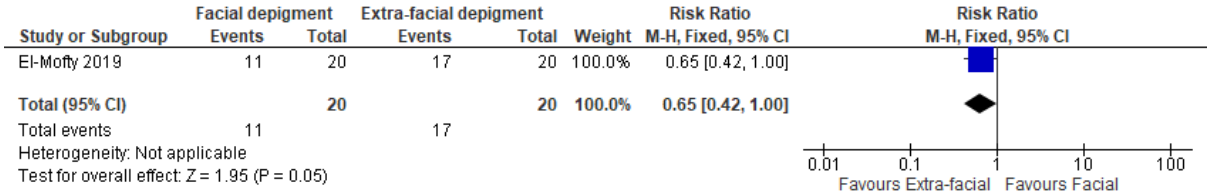


Depigmentation therapies

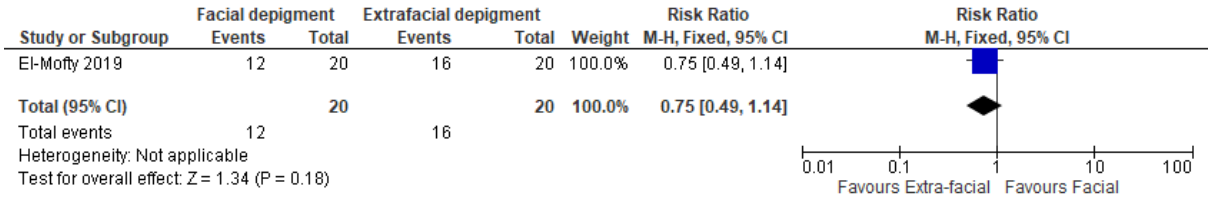
Facial depigmentation vs. extra-facial depigmentation

Critical outcomes

- Depigmentation > 90% in **patients** at 6-month follow-up



- High patient satisfaction in **patients** at 6-month follow-up



Appendix C: Linking Evidence To Recommendation (LETR)

REVIEW TITLE/QUESTION: **(Q1)** In people with vitiligo, what is the clinical effectiveness and safety of topical therapies compared with each other, with placebo or combination of topical plus other active therapies? **(Q3)** In people with vitiligo, what is the clinical effectiveness and safety of systemic therapies compared with placebo, other active therapies, or combination of systemic plus other active therapies? **(Q4)** In people with vitiligo, what is the clinical effectiveness of a course of light therapy (NB-UVB, PUVA, PUVA-sol) compared with each other, other active therapies, placebo or combination of light therapy plus other active therapies? **(Q5)** In people with vitiligo, what is the clinical effectiveness of a course of laser or excimer light therapy compared with each other, other active therapies, placebo or combination of laser or excimer light therapy plus other active therapies? **(Q7)** In people with vitiligo, what is the clinical effectiveness and safety of one combination therapy compared to another combination? **(Q8)** In people with vitiligo, what is the clinical effectiveness and safety of surgical therapies compared with placebo or other treatments? **(Q9)** In people with vitiligo, what psychological interventions are available and what is the effectiveness of these psychological interventions compared with other treatments? **(Q10)** In people with vitiligo, what is the clinical effectiveness of skin camouflage compared with placebo, other interventions or combination of skin camouflage plus other active therapies? **(Q11)** In people with vitiligo, what is the clinical effectiveness complementary therapies compared with placebo, other interventions or combination of complementary therapies plus other active therapies?	
Relative values of different outcomes	The GDG considered the following outcomes for Q1, Q3, Q4, Q5, Q7, Q8, Q9, Q10, Q11: **Critical** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) **Important**

	• Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
	Ranked outcomes according to our guideline development protocol[1] which uses the GRADE methodology (9-7 Critical for decision making; 6-4 Important but not critical for decision making; 3-1 not important for decision making), as agreed between clinicians and patients.
REVIEW TITLE/QUESTION: **(Q2)** In people with vitiligo, what is the clinical effectiveness and safety of depigmentation treatment compared with other active treatments or placebo?	
Relative values of different outcomes	The GDG considered the following outcomes for Q2: **Critical** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Degree of depigmentation (9) • Patient rating of appearance (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) **Important** • Risk of re-pigmentation (6) • Tolerability/burden of treatment (5)
REVIEW TITLE/QUESTION:	

<table>
<tr><td colspan="2">(Q6) In people with vitiligo, who have received large doses of PUVA (more than 150 treatment sessions) or NB-UVB (more than 150 treatment sessions), what is the risk of developing premalignant or malignant skin changes compared with people who have not received light therapies and which individuals are at a particular risk?</td></tr>
<tr><td>Relative values of different outcomes</td><td>The GDG considered the following outcomes for Q6:

Critical
• Melanoma
• SCC

Important
• Basal cell carcinoma
• Other skin cancers
• Intraepidermal carcinoma (Bowen’s disease/SCC in situ)

Less important
• Actinic keratoses</td></tr>
<tr><td colspan="2">The wording for recommendations is standardized so that they are clearly identifiable, unambiguous and specific:
“Offer[1]” or “Do not offer” (strong recommendation ↑↑ or ↓↓) [an intervention] to patients with [skin disease] + [any relevant conditions]
- [1]or similar, e.g. “Use”, “Provide”, “Take”, “Investigate”, etc.)
“Consider” (weak recommendation ↑) [an intervention] for patients with [skin disease] + [any relevant conditions]
The GDG is aware of the lack of high-quality evidence for some of these recommendations, therefore strong recommendations with an asterisk (*) are based on available evidence, as well as consensus and specialist experience.</td></tr>
<tr><td>Balance between desirable and undesirable effects</td><td><u>Summary of included systematic reviews</u>
A total of eighteen systematic reviews were identified and found eligible for inclusion.[2-19] (see Appendix E)
The main findings include:
• A combination of various treatments with light or laser therapy is an effective treatment for vitiligo[2] [12,14-19].</td></tr>
</table>

- In particular, a combination of topical calcineurin inhibitors with excimer laser/light is more effective than laser/light/calcineurin inhibitor monotherapy[4,15,16,19], but its use is cautioned due to the risk of skin cancers.[10]
- Excimer laser (308 nm) showed equivalent efficacies to 308 nm excimer lamp and NB-UVB concerning repigmentation rate.[5]
- There is a lack of high-quality studies investigating micropigmentation, depigmentation, and cosmetic camouflage.[2]
- Natural health products such as Gingko biloba could provide beneficial results in combination with light therapies[2] or as monotherapy[8], but further investigations are necessary.
- Chinese herbal medicines have shown some effectiveness when combined with NB-UVB, but the evidence is limited due to the short follow-up period and low quality of the trials.[7]
- The use of fractional CO_2 in combination with conventional treatments may be considered as a safe adjunct therapeutic option for adult patients with refractive non-segmental vitiligo.[9,12,18] however, heterogeneity was high amongst the included studies. Future research is needed to investigate the interaction between ablative therapy and conventional treatments for vitiligo.
- Topical calcineurin inhibitor monotherapy is effective on the face and neck, especially in children, therefore is a potential treatment option in children where phototherapy is not suitable [16]

One systematic review publication covering the effectiveness and safety of corticosteroids (oral and topical), oral levamisole, topical immunomodulators, topical vitamin D analogues, PUVA (oral and topical) and NB-UVB formulated treatment recommendations for adults and children.[3]

Summary of included comparative studies

A total of 57 comparative studies[20-76] (44 RCTs involving 2809 participants and 14 cohort studies involving 1503 participants) were included (see Appendix E). The sample size of the studies was of a small to large range (15-470 participants) and the range of follow-up was short (1-12 months).

Of the 57 comparative studies, 49 studies reported outcomes with extractable data that was inputted into RevMan.[20-32,34-40,45-50,53-74,76] The remaining eight studies were summarised and not included in quantitative analysis (see Appendix F).[33,41-44,51,52,75]

It was only possible to pool the results of two studies [59,60], this was due to the heterogeneity of interventions, outcomes, and follow-up time amongst the studies; only single-study forest plots were produced for the remaining included studied. Additionally, many of the forest plots showed imprecision due to the small sample sizes and large confidence intervals; this resulted in a downgrading of the quality of evidence (see GRADE tables – **Error! Not a valid bookmark self-reference.**)
Twentyone of the 49 studies showed outcomes with statistically significant results ($p<0.05$; test for overall effect) when inputted into RevMan.[20,23,27,30,38,47,49,53,54,57,59,60,62,65,67-69,72,73,76]

Summary of included within-patient studies

A total of 54 comparative within-patient studies[77-116 102,117-128] (33 RCTs involving 1,260participants and 21 non-randomized cohort studies involving 648 participants) were identified investigating topical, combination, complementary, light, and surgical therapies (See Appendix G**: Narrative findings from within-patient studies**). The sample size of the studies was of a very small to moderate range (9-135 participants) and the range of follow-up was short to moderate (2 weeks – 15 months).

It was not possible to extract data from within-patient studies into RevMan to produce forest plots as the unit of randomization is one half of each participant. The number of patients involved, i.e. the denominator, would have been doubled and any pooled estimate of effects underestimated. However, it was possible to calculate the risk ratio and standard error for two outcomes (repigmentation ≥ 75% and repigmentation ≥ 50%) from two within-patient studies.[81,97]

Summary of included non-comparative studies

As some review questions lacked higher quality evidence (RCTs and cohort studies), lower quality non-comparative studies were included (except for laser and light monotherapy where there are sufficient comparative studies).
A total of 41 non-comparative studies[12,129-165 166] (25 prospective case series involving 2,750 participants; 14 retrospective case series involving 1864 participants; one case study involving two participants; one case report) were identified investigating topical, depigmentation, systemic, combination, surgical, complementary, skin camouflage therapies (see **Error! Reference source not found.**). The sample size of the studies was of a very small to high range (1 – 854 participants) and the range of follow-up was short to long (6 weeks – 6 years).

Topical therapies

	There is a lack of high-certainty evidence for the use of topical therapies for vitiligo. In total, six systematic reviews investigating topical therapies were identified.[2-4,12] All four systematic reviews showed topical therapies in combination with other therapies, particularly light or laser, to be better ($p<0.05$) at achieving repigmentation compared with topical monotherapies (see Appendix E).[2-4,12,15,16] The Cochrane review[2] reported that side effects including folliculitis, acneiform lesions, hypertrichosis, itching, redness, telangiectasia, skin thinning, and atrophy were more common with the use of topical corticosteroids. Combination therapies such as a topical intervention with light therapy seemed to increase repigmentation. One systematic review[3] included children with vitiligo and reported improvement in achieving ≥75% repigmentation at 6 months with clobetasol propionate compared with placebo ($p<0.05$). Despite a lack of evidence about the benefits of different strengths of corticosteroids to use topically, the consensus from the review was that potent or very potent topical corticosteroids should be considered first-line therapy in adults or children, except in long-standing lesions; long-term therapy could lead to side effects of atrophy, striae, and telangiectasia. Based on observational studies in adults, the authors suggested that topical immunomodulators may be equally efficacious to topical corticosteroids; there was there was insufficient evidence to recommend calcipotriol in adults, children or young people. Another systematic review included eight RCTs[4]. A total of three analyses showed that topical calcineurin inhibitors, vitamin D3 analogues, or corticosteroids in combination with excimer laser/light therapy were better at achieving ≥ 75% repigmentation compared with excimer laser/light therapy alone ($p<0.05$). Furthermore, another systematic review[12] showed that CO_2 laser in combination with conventional therapies (topicals/UVB/sun exposure/surgery) was better ($p = 0.03$) at achieving > 50% repigmentation compared with conventional therapies alone. Two systematic reviews [15,16] investigated the use of calcineurin inhibitors in combination therapy compared with calcineurin inhibitor monotherapy. Calcineurin inhibitors were shown to be effective as a monotherpapy on the face and neck in children[16] There was some evidence to suggest that topical calcineurin inhibitors in comination with phototherapy have a synergistic effect, but it is difficult to draw solid conclusions due to the heterogeneity and high risk of bias associate with the studies included in the systematic reviews.

	A total of 28 additional comparative studies[20-23,41,46-48,54-56,59,60,64,70,77-88,100] of these studies, 14 were within-patient studies[77-88,100,110] and four non-comparative studies[129,130,143,144] were identified from the search. The results from the comparative studies, in general, showed that combination treatments including topical therapies were more successful at achieving repigmentation compared with topical monotherapies ($p<0.05$) in six studies[20,23,54,59,60,77] (see Appendix E). There has been new interest regarding the use of Janus Kinase inhibitors for vitiligo. Two of the non-comparative studies investigated the use of ruxolitinib 1.5% cream.[129,130] Both studies revealed that patients experienced some repigmentation, with improvement for facial vitiligo ($p<0.05$). But these studies had a small sample size of eight and twelve patients (see Appendix H**: Narrative findings from non-comparative studies**). Based on the evidence, topical corticosteroids would be a sensible first-line therapy, though limited by their potential side effects. Topical calcineurin inhibitors could be used as an alternative to reduce side effects, especially in areas where these are more likely to occur, such as the face; but the optimal regimen cannot be defined based on the evidence. Several other agents have been investigated for treatment of vitiligo, but generally the evidence is weak, so preventing the GDG from making recommendations for specific topical therapies. However, there is a suggestion that where topical therapies alone fail to increase repigmentation, the addition of light therapy is a sensible next step. **Recommendation ↑↑:** Offer a potent or very potent topical corticosteroid once daily to minimize potential side effects to people with vitiligo as the first-line treatment in primary or secondary care, avoid periocular area. **Recommendation GPP:** Discuss with people with vitiligo the amount of topical corticosteroids to be used, the site of application, and the safe use of a potent or very potent topical steroid when used correctly. **Recommendation ↑:** Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo as an alternative to potent or very potent topical corticosteroids. **Recommendation ↑:** Consider topical tacrolimus 0.1% ointment twice daily under occlusion on photo-exposed areas only in people with non-facial vitiligo as an alternative to potent or very potent topical corticosteroids.

Recommendation GPP: Consider an intermittent regimen of once daily application of potent or very potent topical corticosteroids with or without topical calcineurin inhibitors (more evidence for tacrolimus), factoring the risks and benefits, in people with vitiligo especially in areas with thinner skin, e.g. periocular region, genital area and skin flexures. Examples of intermittent regimens would include:

- 1 week of potent or very potent corticosteroids and at least 1 week off
- 1 week of potent or very potent topical corticosteroids alternating with ≥ 1 week of topical calcineurin inhibitor.

Topical corticosteroids could be used for longer than 1 week in the intermittent regimen, after consideration of the risks and benefits.

Recommendation GPP: Reassess the use of topical treatments (R10-R14) every 3-6 months in people with vitiligo to check for improvement. The use of periodic medical photographs may help assess these changes.

Θ There is insufficient evidence to recommend topical vitamin D analogues in people with vitiligo.

Future Research Recommendation: Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of topical JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.

Depigmentation

The evidence for depigmentation therapies is very limited, the identified systematic reviews did not include studies investigating depigmentation therapies, and the GDG identified only one comparative study. [61] There were five non-comparative studies identified,[131-135] four of which investigated the use of lasers[131-133,135] (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**).

The difference between facial and extra-facial depigmentation was assessed in one comparative study (n= 40).[61] Extra-facial depigmentation [Phenol peel 88%/Cryotherapy/Q-switched (QS) Nd:YAG laser] was shown to be more effectiveve at achieving > 90% depigmentation than facial depigmentation using trichloroacetic acid (TCA) in combination with Qs Nd:YAG (TCA peel 25%/TCA peel 50%/Qs Nd:YAG laser) (p=0.05) and higher overall patient satisfaction.[61]

	Data from the four studies[131-133,135] identified that the use of lasers ranged from QS ruby laser, QS Nd:YAG laser or a 20 to 755 nm laser. The mean duration of follow-up ranged from 13 to 36 months. The median number of sessions to achieve a complete depigmentation ranged from one to six sessions.[131-133,135] One study (n=53) showed, monobenzyl ether of hydroquinone to be effective at depigmenting the skin, but the repigmentation was high (78%) after the end of treatment in patients who had achieved successful depigmentation. Patients were followed-up from onset of treatment for an average of 5.4 years; the two commonest side effects included a noxious sensation and an irritant dermatitis.[134] One study (n=22) assessed cryotherapy and/or 755nm laser therapy; depigmentation varied according to body site with better results on the trunk and worse on the peripheries (p=0.013).[135] A study (n=15) investigating the use of QS Nd: YAG laser at 532-nm wavelength found > 90% resolution of pigmentation in 13 of 15 patients, these patients did not experience relapse at 3-month follow-up.[133] Laser assisted depigmentation with QS laser achieved complete depigmentation in all patients, however the sample size was small (n=6) and included females only. One third of the patients had no relapse, complete repigmentation was observed after 21 months in one patient. Side-effects were limited to transient purpura and crusts. In another small study (n=7), 48% of the 27 included patients treated with QS laser showed ≥75% depigmentation, and the results were better in patients with active disease than those with stable disease (p=0.046).[132] **Recommendation GPP:** Consider depigmentation therapies in people with extensive vitiligo on visible sites, in whom the condition is having a negative psychological impact. This should be done after adequate psychological assessment and/or intervention. Please refer to the supplementary information document for further details. **<u>Systemic therapy</u>** There is a notable lack of evidence for the use of systemic therapies for vitiligo. Only a very small number of poor-quality studies reporting a variety of outcome measures, and mainly using systemic therapies in combination with other modalities were identified.[24,25,147,148,167] The Cochrane systematic review identified 13 studies examining systemic therapies for the treatment of vitiligo.[2] Analysis of three RCTs were reported for treatments and outcomes relevant to this guideline. One RCT (n= 86) showed that weekly oral minipulse therapy (OMP) of betamethasone 0.1 mg/kg of body weight on two consecutive days for 3 months then tapering of the dose by 1 mg/month over 3 months, in combination with NB-UVB, was better at achieving ≥75% repigmentation than

	OMP alone [RR= 7.41 (95% CI, 1.03 – 53.26), p=0.014].[168] This was not the case for OMP in combination with PUVA or BB-UVB versus OMP alone. Adverse events included weight gain in 37%-50% of patients in both groups. The second RCT (n=60) showed that azathioprine plus PUVA to be better at achieving≥75% repigmentation than azathioprine alone (9 patients in combination group versus 0 in PUVA alone) [RR=17.77 (95% CI, 1.08 – 291.82), p=0.002].[169] Adverse events included gastric upset in two patients on azathioprine. No cases of malignancy were seen up to 2 years follow-up. The third RCT did not report on repigmentation.[170] The study assessed the effect on QoL, which found no statistically significant difference in DLQI improvement with the addition of oral levamisole to topical mometasone furoate compared with oral placebo plus topical mometasone furoate. We identified two further RCTs, not included in the Cochrane review from our search.[24,25] One study (n=50) of minocycline 100 mg daily compared with dexamethasone OMP 2.5 mg on 2 consecutive days a week showed minocycline to be slightly better but this was not statistically significant [RR=3.00 (95% CI, 0.33 – 26.92), p=0.33].[24] Adverse events were common in both groups (20-28%) including hyperpigmentation in the minocycline group and weight gain in the steroid group. In the second study (n=52) there was a similar reduction in the vitiligo diseases activity score for methotrexate and dexamethasone OMP; the authors concluded that both drugs demonstrated equal efficacy.[25] Adverse events were common in both; some patients treated with methotrexate experienced nausea and some of those treated with dexamethasone experienced weight gain and acne. Recent reports have suggested that the new JAK inhibitor, tofacitinib, may be effective for vitiligo. Three studies of very low-quality investigating tofacitinib were identified, including a total of 13 patients.[147,148,167] The largest series of 10 patients[147] showed a small mean decrease in body surface area (BSA) affected with vitiligo, particularly in areas exposed to the sun or NB-UVB. A further report of two patients treated with oral tofacitinib in combination with NB-UVB showed ≥75% repigmentation,[12] and a case report of tofacitinib monotherapy showed partial repigmentation. No adverse events were identified other than respiratory tract infection in two patients. In summary, there is currently very poor evidence for systemic treatment in vitiligo. OMP steroid in combination with NB-UVB may have an additional benefit compared with NB-UVB alone but must be balanced against a significant risk of side

	effects. Azathioprine in combination with PUVA may be beneficial[171] but the Summary of Product Characteristics (SmPC) for azathioprine states that 'An increased risk of skin tumours have occurred in patients during treatment with azathioprine' and that 'Patients should be warned about undue exposure to the sun or UV rays.' The GDG feels that the risk of potential malignancy is too high to recommend this combination. The studies above did not include children or did not analyse children separately. Safety concerns of systemic treatment, including OMP steroids are greater in children than adults. **Recommendation ↑:** Consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg/month for a further 3 months in combination with NB-UVB in people with rapidly progressive vitiligo to arrest activity of the disease after careful consideration of risks and benefits (see R18). **Recommendation↓↓:** Do not offer azathioprine in combination with PUVA (and NB-UVB) to people with vitiligo due to the risk of malignancy. **Recommendation GPP:** Consider an equivalent dose of alternative oral corticosteroids in people with rapidly progressive vitiligo if betamethasone is not available. **Θ** There is insufficient evidence to recommend any currently available systemic treatments as monotherapy for people with stable vitiligo. However, there is some evidence for their use in combination with other treatments for rapidly progressive vitiligo (see R17 and R18). **Θ** There is insufficient evidence to recommend minocycline, methotrexate or tofacitinib for people with vitiligo. **Future Research Recommendation:** Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of oral JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.

Light and laser therapy

NB-UVB

NB-UVB was introduced for the treatment of non-segmental vitiligo (NSV) in 1997 when it was shown to be as efficient as topical PUVA with fewer side effects.[33] Since then, it has replaced PUVA as the preferred phototherapy choice. NB-UVB is at least as effective as PUVA in treating vitiligo.[172] The match of repigmentation to healthy skin colour is better with NB-UVB than with PUVA.[173] Moreover, NB-UVB has been shown to be more effective at achieving >50% repigmentation and at inducing repigmentation in unstable vitiligo compared with PUVA.[26]

A meta-analysis showed that there was no statistically significant difference between NB-UVB and 308 nm excimer laser in achieving ≥ 75% or 100% repigmentation (p>0.05). More patients achieved ≥ 50% repigmentation with 308nm laser than with NB-UVB treatment, but the risk ratio was small [two studies, RR=1.39, (95% CI 1.05-1.85); p=0.002].[5]

The Cochrane systematic review included several RCTs which assessed NB-UVB as monotherapy and in combination with other treatments.[2] Generally, the Cochrane review showed NB-UVB in combination with other therapies to be more effective than NB-UVB monotherapy at achieving ≥ 75%. The combination of NB-UVB with antioxidant pool (alpha lipoic acid, vitamin C, E and fatty acids) seems to be more effective in achieving ≥75% repigmentation than NB-UVB alone (p<0.05).[174]

The combination of NB-UVB with topical pimecrolimus was more effective in achieving ≥75% repigmentation of the facial lesions than NB-UVB with placebo (p<0.05); there was no statistically significant difference between the two groups on other body areas.[175] The combination of NB-UVB with oral vitamin E was shown to be slightly better but not statistically significant in obtaining >75% repigmentation than NB-UVB alone.[28]

A combination of NB-UVB with topical calcineurin inhibitors (meta-analysis; two studies) or topical vitamin D3 was slightly better at achieving ≥75% repigmentation, but this was not statistically significant.[10] A more recent systematic review has shown that topical NB-UVB in combination with topical calcineurin inhibitors [3 studies, RR=1.79, 95% CI (1.06 - 3.01), p=0.03] or 5-FU injection [1 study, RR=7.25, 95% CI (2.71 - 19.36), p<0.0001] or ER: YAG laser ablation and topical 5-FU in combination with NB-UVB [1 study, RR=5.60, 95% CI (2.31 - 13.59), p=0.0001] or CO_2 laser [2 studies, RR=7.00 (1.30 - 37.60), p=0.02] is superior to NB-UVB monotherapy at achieving ≥75% repigmentation.[19] An additional systematic review conducted in 2020 has also shown that tacrolimus in combination with NB-UVB is slightly better at achieving ≥75% repigmentation [2 studies, RR 1.34; 95% CI (1.05 – 1.71), p=0.02].[15]

	An additional 18 comparative studies[26-29,34,62,66,73,91,94,95,103-105,109,110,118,120,122] were identified that were not included in the systematic review or reported outcomes not covered by the included systematic reviews. Ten of the 19 additional studies were within-patient studies.[91,94,95,103-105,109,118,120,122] Six of the ten within-patient studies showed NB-UVB in combination with another therapy provided more effective repigmentation than NB-UVB monotherapy; one study (n=20) recruited children (5-14 years old) and showed NB-UVB in combination with tacrolimus 0.03% ointment compared with NB-UVB monotherapy was slightly better but not statistically significant at achieving >50% or >75% repigmentation.[103] One within-patient study (n=25) showed that NB-UVB in combination with topical calcipotriol did not result in greater repigmentation when compared with NB-UVB therapy alone.[109] Of the remaining six studies,[26-29,34,62] three studies[28,34,62] showed combination treatment with NB-UVB compared with NB-UVB monotherapy was slightly better but not statistically significant at achieving ≥50% and ≥75% repigmentation. One study (n=55) evaluated repigmentation using the VASI, combination of afamelanotide implant with NB-UVB was superior to NB-UVB alone ($p<0.05$);[29] however, the degree of repigmentation improved in both treatment groups ($p<0.001$). A further pilot study (n=29) showed hand-held NB-UVB home phototherapy compared with placebo was slightly better but not statistically significant at achieving ≥ 75% repigmentation at 4 month-follow-up.[27] The side effects of NB-UVB include erythema, mild burning or pain, pruritus, and dry skin;[6,27,95] these were reported to be well-tolerated by most patients and generally disappeared several hours after treatment. Other side effects included perilesional pigmentation, hyperpigmentation, ecchymosis, and cold sores.[27,176] There is a lack of studies on NB-UVB in children. This is an issue of concern as vitiligo often starts in childhood and early treatment seems to be more effective. However, NB-UVB started early in life is more likely to be associated with a higher cumulative dose and a higher total number of treatments. The maximum number of NB-UVB sessions remains an open question as there is no evidence from the current literature that the skin cancer risk is increased in treated patients.[177-179]

	The majority of data is from the retrospective studies on psoriasis patients treated with NB-UVB. The GDG has not found any evidence to suggest that there is an increased risk of skin cancer with NB-UVB; there is a need for long-term follow-up studies of vitiligo patients treated with NB-UVB to establish if the incidence of skin cancer may be increased. **Recommendation ↑↑:** Offer NB-UVB (whole body or localised, e.g. home-based hand-held) as first-line phototherapy to people with vitiligo who have an inadequate response to topical therapy and/or with extensive or progressive disease. This may be combined with topical calcineurin inhibitor[†] (more evidence for tacrolimus) or potent topical corticosteroid,[‡] for localised sites. Counsel patients on the significant risk of loss of response upon treatment cessation. [†] Prior to combination NB-UVB and topical tacrolimus treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. A shared decision should be made with the person with vitiligo, taking into account other alternatives, the individual's personal and family history of skin cancer risk and the impact of the vitiligo. [‡] The evidence for potent topical corticosteroid is limited. Prior to this combination, consider the risk/benefit ratio of the prolonged use of potent topical corticosteroid. **Future Research Recommendation:** A prospective, randomized controlled trial evaluating the safety and efficacy of topical tacrolimus combined with NB-UVB compared with commonly used interventions. **Recommendation GPP:** Inform people with vitiligo who are eligible for NB-UVB of the requirements (depending on local protocols: a pre-therapy assessment, medical photographs taken prior to and during follow-ups 3-6 months, two to three sessions weekly possible for up to 1 year), and the likely response depending on the affected anatomical site (e.g. the face and trunk usually achieve better repigmentation than acral sites). Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com. **PUVA** In total, four systematic reviews investigated the use of PUVA in treating vitiligo were included.[2,3,6] A meta-analysis of three studies from the Cochrane review showed an increase in the proportion of patients achieving >75% repigmentation in favour of NB-UVB compared with oral PUVA, but also an increase in the number of patients experiencing

	adverse effects such as nausea (p<0.05), erythema (p<0.05) and itching associated with NB-UVB compared with oral PUVA.[2] Moreover, a meta-analysis of two studies reported by another systematic review[6] showed NB-UVB compared with PUVA to be slightly better but not statistically significant at achieving >50% or >75% repigmentation. Side effects reported included mild-to-moderate itching, sedation, xerosis, exacerbation of acne lesions, and nausea. One systematic review[3] formulated treatment recommendations for adults and children. The authors came to the consensus that oral PUVA is an effective treatment for vitiligo in adults, and although topical PUVA is associated with fewer adverse effects, it is unlikely to be an effective treatment for vitiligo in adults. The authors did not recommend PUVA for children under the age of 12 due to a risk of cataract formation, and an increased risk of skin cancer.[3] An additional five comparative studies[31,33,41,54,93] were identified from the search. A single-centre RCT (n=60) investigated PUVA in combination with topical calcipotriol compared with topical calcipotriol monotherapy; combination therapy was better at achieving ≥75% repigmentation at 6-month follow-up (p=0.008).[54] Erythema, pruritus, burning, nausea, and vomiting were associated with PUVA in combination with calcipotriol.[54] A non-randomized comparative study[31] (n=35) showed oral PUVA to be associated with a better improved QoL compared with PUVAsol (p=0.04) and slightly better but not statistically significant at achieving ≥50% and ≥75% repigmentation at 36-week follow-up.[31] A further, non-randomized comparative study investigating a group of patients with vitiligo (n=106) showed 311 nm UVB therapy to be more effective than topical PUVA at achieving repigmentation at 4-month follow-up, however the percentage repigmentation was not reported.[33] Another non-randomized comparative study (n=26) compared calcipotriol monotherapy to calcipotriol in combination with PUVA therapy. But it is difficult to draw conclusions from this study due to various follow-up times, small sample size, and lack of reported data suitable for statistical analysis (see forest plots in Appendix B**: Forest plots**).[41] A within-patient, non-randomized trial (n=23) showed calcipotriol in combination with PUVA to be slightly better but not statistically significant at achieving a marked response (>50% repigmentation) compared with PUVA monotherapy.[93] **Recommendation ↑:** Only consider PUVA/PUVAsol in adults with vitiligo if treatment with NB-UVB is unavailable or has been ineffective. [§] § For contraindications refer to BAD PUVA guidelines 2016[172]

The following is guidance from the British Photodermatology Group and the BAD relating to cancer surveillance with the use of UVB and/or PUVA treatment:

"There are no limits to the numbers of treatments patients may have. However, the figures of >200 PUVA and >500 UV treatments are thresholds to trigger skin cancer screening review. There will be patients in whom it is clinically appropriate to continue to treat beyond these numbers. Decisions about whether to continue to treat past these arbitrary threshold numbers are the responsibility of the Dermatology Consultant. The Dermatology Consultant must assess the relative risks and benefits of the various treatment options available for each patient. In some patients, the correct decision is to continue beyond these arbitrary threshold figures." (2016, Phototherapy Service Guidance, pg. 35)

Risk of developing premalignant or malignant skin changes in people with vitiligo receiving light therapies

The risk of carcinogenicity in people with vitiligo treated with NB-UVB and PUVA is still unclear. We did not identify any studies investigating the risk of developing premalignant or malignant skin changes in people with vitiligo, who received large doses of PUVA or NB-UVB compared with people who have not received light therapies. The latter prevent the GDG from making recommendations on this question.

Previous research has shown that the absolute increase in risk of developing SCCs following over 150 PUVA exposures increases from 2.7% (for 100-159 exposures) to 8.8% for over 160 exposures in patient with psoriasis. However, three small studies[177,180,181] were unable to detect any definitive increase risk of skin cancer following NB-UVB in psoriasis patients. A larger study of 1380 patients suggested that UVB remains a relatively low-risk treatment for psoriasis.[182]

The GDG would like to make the following suggestions based on the NICE psoriasis guideline[183] and the BAD biologics for psoriasis checklist.[184] The aforementioned documents provide indirect evidence based on data from psoriasis population.

Home phototherapy

There was a lack of high-quality studies investigating the use of home phototherapy for the treatment of vitiligo. The included systematic reviews did not investigate home phototherapy, two studies were identified from the search which investigated home-based phototherapy for the treatment of vitiligo.[32]

	Hand-held home-based phototherapy compared with institution-based excimer lamp was shown to be slightly better but not statistically significant at achieving ≥50% and ≥75% repigmentation at 6-month follow-up. Similarly, the pilot Hi-Light trial showed hand-held home phototherapy compared with placebo was slightly better but not statistically significant at achieving ≥75% repigmentation at 4-month follow-up.[27] The most recent data from the HI-Light trial has shown hand-held home-based NB-UVB phototherapy in combination with topical corticosteroid (mometasone furoate 0.1%) to be superior to topical corticosteroid monotherapy at achieving ≥75% repigmentation at 9 months [1 study, RR=4.45, 95% CI (1.54 – 12.88), p=0.006]; hand-held home-based NB-UVB monotherapy was shown to be superior to topical corticosteroid monotherapy but this was not statistically significant [RR = 2.30, 95% CI (0.72 – 7.34), p=0.16]. Multiple tools were used to assess the QoL but hand-held home-based NB-UVB was not shown to improve the QoL compared with topical corticosteroid monotherapy. Treatment-related adverse events were less in those using topical corticosteroid therapy. Erythema (grad 3 and 4) in particular was shown to be higher in those receiving topical corticosteroids in combination with hand-held home-based NBUVB compared with topical corticosteroid monotherapy in both adults [RR=12.81, 95% CI (3.10 – 52.89), p=0.0004] and children [RR=7.00, 95% CI (0.90 – 54.32)] and similarly higher in those receiving hand-held home-based NB-UVB monotherapy compared with topical steroid monotherapy in both adults [RR=10.23, 95% CI (2.44 – 42.89), p=0.001] and children [RR=7.18, 95% CI (0.93 – 55.68), p=0.06].[76] Considering newly emerging evidence that early treatment of vitiliginous lesions seems to be effective,[185-187] home-based targeted phototherapy is a safe option, if done under supervision of a trained clinician.[27,32] Further high-quality RCTs and economic evaluations are needed to assess the clinical and cost effectiveness of home-based phototherapy. **<u>Laser therapies</u>** Targeted laser phototherapies are used for localised vitiligo, especially for small lesions, to avoid side effects due to whole-body irradiation with NB-UVB. Several studies assessed laser and light therapies as monotherapies, and in combination with topical treatments.[2] In particular, combinations of excimer laser with topical calcineurin inhibitors,[188-191] topical corticosteroids[192] or topical vitamin D3 analogues[193] seem to be more effective in achieving ≥75% repigmentation of vitiliginous lesions than excimer laser alone [RR = 2.57 (95% CI 1.20 – 5.50), p=0.02] and [RR=4.50 (95% CI 1.04 – 19.47), p=0.04] respectively. One RCT (n=233) identified from the search[53] showed yiqiqubai granules in combination with 308-nm excimer laser to be more effective in achieving ≥ 50% repigmentation than yiqiqubai granules alone [RR=1.62 (95% CI 1.13-2.34), p=0.010]. A non-validated 5-point scale was used to assess the QoL; combination therapy of 308-nm excimer laser with yiqiqubai granules was better (p<0.05) than 308-nm laser or yiqiqubai granules monotherapy at improving QoL in the following areas: embarrassment, social, and work.[53]

	A meta-analysis showed 308 nm excimer laser was slightly better but not statistically significant compared with 308-nm excimer lamp in achieving ≥75% or ≥50% repigmentation (p> 0.05).[5] However, more patients (p=0.002) or lesions (p=0.009) achieved ≥50% repigmentation by 308nm laser than by NB-UVB treatment.[5] Side effects of excimer laser include hyperpigmentation, burning, stinging, moderate-to-severe erythema, oedema, and blisters.[2,5,92] Several studies reported data for the use of CO_2 laser in vitiligo.[9,17,18,23,49,123] One RCT (n = 68 patients) showed that in lesions on hands and feet, a combination of CO_2 laser with topical 5-fluorouracil, may be effective for acral, refractory vitiligo in adults unresponsive to other treatments in achieving ≥50% repigmentation [RR=16.80 (95% CI 10.88 – 25.95), p < 0.00001] and ≥75% repigmentation [RR=24.96 (95% CI 14.21 – 43.86), p < 0.00001].[23] In addition, a meta-analysis revealed that using fractional CO_2 laser in combination with conventional treatments was more effective at achieving ≥75% repigmentation [RR = 2.80 (95% CI 1.29 – 6.07), p=0.009], and may be considered as a safe adjunct therapeutic option for patients with refractive non-segmental vitiligo.[9] The most common side effects reported were pain, followed by burning sensation, erythema, oedema and oozing; other side effects included itching and ecchymosis.[9,49] No infection, scarring or Koebner phenomenon occurred after using fractional CO_2 laser.[9] One systematic review [18] showed ablation therapy (CO_2 laser in 10 studies and erbium-YAG in 5 stuidies) in combination with other treatments for vitiligo to be superior to treatment without ablation therapy at achieving ≥75% repigmentation [11 studies, OR=5.812, 95% CI (2.194 – 15.3939), p=0.000] and ≥50% repigmentation [11 studies, OR=10.490, 95% CI (4.632 - 23.757), p=0.000]. Sub-group analysis showed fractional CO_2 laser in combination therapy to be superior to the control at achieving ≥50% repigmentation [6 studies, OR=7.810, 95% CI (1.754 – 34.780), p = 0.007] and marginally superior at achieving ≥75% [5 studies, OR=1.897, 95% CI (0.764 – 4.711), p = 0.168]. Moreover, CO_2 laser in combination therapy was superior to control treatment in achieving ≥ 50% repigmentation [7 studies, OR=9.964, 95 % CI (3.107–31.955, p<0.001] and ≥ 75% repigmentation [6 studies, OR=3.901, 95% CI (0.785–19.383), p=0.096]. Non-fractional erbium-YAG laser combination therapy was shown to be superior to the control group in achieving ≥ 50% repigmentation [2 studies, OR = 20.272, 95% CI (1.953 – 210.459), p=0.012] Finally, the GDG found no consensus on the treatment duration or the maximum number of treatments for laser therapies from the studies identified.

	Recommendation ↑: Consider excimer laser or light in people with localised vitiligo in combination with topical calcineurin inhibitors (more evidence for tacrolimus). Prior to treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest. **Recommendation ↑:** Consider CO_2 laser in combination with 5-fluorouracil in adults with non-segmental vitiligo on hands and feet if other treatments have been ineffective (apply 5-fluorouracil once daily for 7 days per month for 5 months; CO_2 laser treatments once a month for 5 months). This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest. **Θ** There is insufficient evidence to recommend combination treatment of potent or very potent topical steroid with NB-UVB plus CO_2 laser for people with vitiligo. Future Research Recommendation: Prospective, randomized controlled trials evaluating the safety and efficacy of CO_2 laser for vitiligo compared with commonly used interventions in adults with vitiligo. **<u>Combination therapies</u>** Generally, combination therapies were shown in systematic reviews to be more effective at achieving repigmentation compared with monotherapies (see Appendix E).[2,4,7,10,14] These comparisons are considered in other sections, according to the monotherapy comparators. This section deals with studies that compared one combination therapy with another combination therapy. Combination of topical calcineurin inhibitors with ultraviolet and other forms of radiation is generally discouraged[194] due to the theoretical increased risk of skin cancer, although there is no firm evidence for this. None of the combination studies in this systematic review assessed long-term outcomes such as incidence of new skin cancers following treatment, so the GDG recommends that the findings regarding the combination of topical calcineurin inhibitors and excimer laser or light be interpreted with caution. The GDG noted that when comparing one combination treatment with another, the overall quality of studies was poor and there was very little evidence to support one combination over the other.

One RCT (n=50) comparing alpha-lipoic acid with placebo, both combined with betamethasone injections and NB-UVB, showed no statistically significant difference between the two groups in those achieving at least 50% and 75% repigmentation (p>0.05).[36] Nine participants reported nausea or dizziness after taking alpha-lipoic acid, although the time point at which this occurred was not specified (the GDG assumed it was throughout the course of the trial). Seven participants reported weight gain after receiving betamethasone injections, this resolved after cessation of treatment.

One RCT (n=50) compared punch grafting plus PUVA with punch grafting plus topical 0.1% fluocinolone acetonide; PUVA or topical treatment was commenced 4 weeks after punch grafting and treatment was continued for 6 months.[35] Cosmetic acceptability of results at 6 months showed no statistically significant difference between the groups [RR=0.94 (95% CI 0.77 – 1.15), p=0.57]. Adverse events including cobblestoning, infection, and displacement or depigmentation of the grafts occurred in similar rates in both groups.

A non-randomized study compared (n=32) combination treatment involving monochromatic excimer light with either topical 0.1% tacrolimus, topical 4% khellin, or both.[37] This study was of poor quality with a high risk of bias and small sample size; statistical significance was not reached for any of the outcomes analysed (p>0.05).

The GDG identified seven non-comparative studies assessing various other combination treatments for vitiligo (see **Error! Reference source not found.**).[12,149-153,161]These non-comparative studies did not provide robust evidence for any of the combination treatments assessed. The two studies assessing oral methylprednisolone reported gastrointestinal side effects in some participants;[152,153] combination of oral methylprednisolone and topical fluticasone resulted in several cases of cutaneous dermatophyte infections and precipitation of acne.[153] There is some evidence to suggest that the reduction/removal of epidermal H_2O_2 using NB-UVB (0.15 mJ/cm^2)- activated psudocatalase PC-KUS in children is effective at achieving repigmentation in children with vitiligo.[161]

The GDG also identified four within-participant studies assessing combination treatments.[89,90,101,102] One within-patient, RCT (n=25) showed a triple combination of fractional CO_2 laser plus topical betamethasone and NB-UVB to be better (p=0.042) at achieving at least 50% repigmentation compared with fractional CO_2 laser plus NB-UVB only.[89] All participants experienced moderate pain, erythema and oedema due to the laser treatment. A further study (n=26) showed fractional CO_2 laser plus topical 0.05% clobetasol propionate and NB-UVB to be slightly better but not statistically significant at achieving >50%

repigmentation compared with fractional CO_2 laser plus topical 0.05% clobetasol propionate alone. (p=0.065).[90] Participants receiving triple combination treatment experienced more post-treatment pain than the other participants (p<0.001).

Korobko *et al*. (2016)[101] compared microneedling combined with latanoprost 0.001% solution or 0.1% tacrolimus ointment; combination therapy was better that 0.1% tacrolimus ointment monotherapy at achieving ≥75% repigmentation (p= 0.0459).[101] Mina *et al.* (2018)[102] compared microneedling combined with 5-flurouracil or 0.1% tacrolimus ointment. The combination of 5-flurouracil with microneedling was better at achieving repigmentation compared with 0.1% tacrolimus in combination with microneedling (p=0.023). Adverse effects such as hyperpigmentation, inflammation and ulceration were observed in patches treated with 5-fluorouracil while in patches treated with tacrolimus, there were no complications observed (p = 0.004).[102]

Although there was some limited evidence to support the use of some combination therapies, the overall quality of the evidence was very low, and no firm recommendations can currently be made for any combination treatment assessed and discussed above.

Surgical therapies

The GDG noted that due to the invasive nature of the surgical procedure it is difficult to design RCT studies that are truly double blinded with placebo control. As a result, many novel techniques are reported as cohort studies of small sample sizes.

In total 7 RCTs were included.[57-59,62,63,71,72] One RCT compared NCES blister roof graft to NCES Thiersch graft, whilst there was no difference in repigementation achieved, greater hyperpigmentation was associated with the NCES Thiersch graft group [RR=8.20; 95% CI (2.56 – 26.30), p=0.0004] [57] and NCES/non-cultured dermal cell suspension (NDCS) was shown to be marginally better than NCES at achieving ≥ 75% compared with NCES [RR=1.89; 95% CI (1.12 – 3.17), p=0.02]. [72] Combining tacrolimus 0.1% with microneedling was shown to be superior to microneedling monotherapy in achieving repigmentation ≥ 75% [RR=2.00; 95% CI (1.14 – 3.52), p=0.02] and repigmentation ≥ 50% [RR=2.09; 95% CI (1.26 – 3.48), p=0.005] at 3-month post-treatment follow-up.[59]

The GDG identified one systematic review which included studies investigating surgical therapies.[2]

	The review included a wide range of surgical techniques. Overall melanocyte transplantation resulted in a reduction of DLQI scores in patients ($p<0.05$).[31,195] The main side effects of minipunch grafting techniques showed cobblestoning and variegated appearance of scars.[35] Interestingly this study also found no difference between patients with segmental and non-segmental vitiligo, in their respective response rate. The proportion of patients achieving ≥75% repigmantation was higher in those with blister grafts.[196] Dermabrasion and needling were reported as treatment but without any relevant data to report. One non-randomized, within-patient study (n=83) compared blister roof grafting (BG), cultured melanocytes transplantation (CMT), and NCES transplantation in the treatment of stable vitiligo.[98] Excellent repigmentation (≥90%) was observed in all treatment methods at 12-month follow-up, with a higher proportion in those receiving BG (76%) compared with CMT (55%) and NCES (53%) ($p=0.038$, $p=0.017$, respectively). The study concluded that all methods were effective in treating vitiligo. However, the donor size to treatment area ratio varied according to procedure; BG was used to treat much smaller areas at a ratio of 1:1 as opposed to 1:5 for NCES, hence, a like-for-like comparison was not made for the treatment areas, as agreed by the GDG. The treatment was well tolerated; none of the patients developed infection, milia, or visible scarring at any donor or recipient site – this could have been due to the use of CO_2 laser for dermabrasion. Another non-randomized, within-patient study (n=10) treated, in total, 39 patches in patients with stable, generalized vitiligo.[99] Nine were treated by melanocytes-keratinocytes transplantation (MKT) alone; ten patches were treated with MKT and excimer laser; another ten treated with excimer laser alone; and ten patches were treated as the control with manual dermabrasion only. At 2-week follow-up, 2/9 patches in the combination group (MKT and laser) showed ≥90% repigmentation, whereas the other groups did not reach this level of pigmentation. The authors conceded that the repigmentation rate is lower for MKT alone than in other reports, they concluded that despite a small sample size there is value of adding MKT to excimer laser ($p<0.001$). The small sample size and short follow-up period is a limitation of this study; therefore, the results should be interpreted with caution. A multicentre, non-randomized comparative study (n=170) focused on comparing lesion stability with disease stability.[39] Patients with lesion stability (greater than 12 months) and disease stability of only 6 to 11 months were shown to have similar response to various surgical methods [mini-punch grafting (MPG), ultrathin skin grafting (UTSG), and NCES] to patients with overall disease stability of greater than 12 months. This suggests that patients may be able to have surgical treatment earlier if certain lesions are stable, despite their overall disease being progressive. The percentage of patients

achieving > 90% repigmentation at 6 months was 45%, 42% and 30% in the NCES, UTSG, and MPG groups, respectively. The number of non-responders (13.3%) was the highest in the MPG group. Adverse effects included perigraft halo and hyperpigmentation.

A further five, more recent within-patient studies were identified[111-115] investigating microneedling, NCES, NCES in combination with follicular cell suspension (FCS), and melanocyte keratinocyte transplantation (MKTP). But these were of a small sample size and the GDG did not think the evidence was sufficient to make any recommendations.

None of the studies listed assessed the change in patients' QoL as a result of treatment; the GDG considered that percentage repigmentation is only one objective measure of successful therapy.

Recommendation ↑: Consider cellular grafting, e.g. blister grafting or cell suspension, in people with stable, segmental or non-segmental vitiligo that is unresponsive to other treatments, and who remain distressed by the condition. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.

Θ There is insufficient evidence to recommend mini-punch grafting in people with vitiligo.

Psychological therapies

There is a dearth of studies that have sought to examine the effectiveness of psychological therapies, interventions, or techniques for the alleviation of distress associated with vitiligo or to facilitate adjustment to the condition.

The Cochrane systematic review[2] identified two RCTs examining psychological therapies in patients with vitiligo.[42,43] One of the RCTs (n=16) showed that weekly one-to-one cognitive behavioural therapy (CBT) for 8 weeks was better at improving psychometric measures of body image, QoL, and self-esteem compared with the control group receiving no change in conventional treatment, at 5-month follow-up ($p<0.05$).[42] Twelve participants were eligible to have the progression of their vitiligo assessed through photographs (four were ineligible as they were receiving PUVA treatment, and the others did not consent to be photographed). Independent clinician and researcher ratings indicated changes in five cases, improvement in three CBT cases, and deterioration in two participants in the control group. Clearly, the findings in relation to progression of vitiligo whilst interesting are essentially anecdotal.

	Another RCT (n=44) compared eight session group interventions; two parallel groups of CBT and group person centred therapy (PCT) with a control condition within a hospital and community setting.[43] Both active treatments led to significant improvements in comparison to the control group but only on the general health questionnaire, and the interventions were thus judged to be unsuccessful. The other clinical measures which included outcomes such as self-esteem and body image, in addition to disease progression (again measured by review of photographs), did not show improvement. For the CBT groups, improvement in the general health questionnaire were noticeable directly post-treatment and maintained over the duration of the follow-up, whereas for PCT, improvements were only visible at 6-month and 12-month follow-up. One further RCT[44] and one non-comparative prospective case series[146] not included in the Cochrane systematic review, were identified from our search. The RCT (n=75) compared self-help interventions (administered as pdf leaflets) with a control (no counselling and change in treatment) within a community setting.[44] There were two intervention groups which used CBT techniques to target socially related concerns; one of the interventions was enhanced with a behaviour change technique aimed at facilitating the use of the CBT techniques. A higher percentage of participants showed a reliable change in the enhanced self-help condition compared with the other intervention and control group in the primary outcome measure (a measure of social anxiety) but not in the other outcome variables, which included measures of anxiety, depression, and body image concern. Qualitative feedback on the intervention indicated that participants had found the self-help materials in both active treatment groups useful. There was an overall improvement in mood charts in seven of the eight patients, one patient had worsening of mood scores due to an increase in number of lesions. The non-comparative study (n=13) used five sessions of CBT through five weekly sessions conducted by a dermatology trainee under the guidance of a clinical psychologist.[146] All eight patients who completed the five sessions had a reduction in DLQI, this was meaningfully different in four patients at the end of the five sessions and at 12-week follow-up. Five of the eight patients had meaningful reductions in Skindex-16 scores at the end of the five sessions and at 12-week follow-up. The Cochrane review and our own analysis identified significant limitations with all studies in terms of risk of bias. For example, the Papadopoulos *et al.*[42] study was unable to employ any robust blinding, additionally it only compared an active psychological treatment with receipt of no treatment at all.[42] The Papadopoulos *et al.* (2004)[43] and Shah *et al*. (2014)[44] studies similarly had significant limitations, although they both had active psychological treatment comparison groups as well as control conditions.[43,44]

Caution is needed in extrapolating recommendations from these studies given the limitations in both study design and the lack of replication. Despite the limitations within the evidence base, the GDG remains of the opinion that conducting a psychological screening assessment within all levels of care (including within general practice) and providing access to psychological intervention remains an important consideration in the treatment of vitiligo, particularly in secondary care centres where psychological distress may be higher. This opinion is supported by the outcome of the James Lind Alliance Priority Setting Partnership which identified psychological intervention as a priority area.[197] Clinicians should also consider using brief measures of psychological distress in conjunction with vitiligo specific QoL measures such as VitiQoL and VIPs (vitiligo impact patient scale).[198]

The evidence suggests that people with vitiligo experiencing psychological distress or/and an adverse reaction on their QoL might benefit from psychological interventions delivered within a stepped a care model. Some people might benefit from self-help or guided self-help, whereas other people may require one-to-one therapy or benefit from group intervention.

Recommendation ↑↑: Offer* information on self-help (e.g. leaflets, books, websites, apps) to people with vitiligo with mild psychological distress.

Recommendation ↑↑: Offer* referral to psychological services for group or/and individual cognitive behavioural therapy (CBT) to people with vitiligo with moderate-to-severe psychological distress.

Future Research Recommendation: Prospective randomized controlled trials evaluating the effectiveness of psychological interventions in people with vitiligo.

Skin camouflage

There were no systematic reviews identified which assessed cosmetic camouflage therapies. In total, there were five studies identified which assessed camouflage therapies in patients with vitiligo.[40,45,137,138,199] The only relevant outcome measure from these studies was change in QoL.

	One RCT (n=144) was identified comparing herbal Iranian skin camouflage preparation with Exuviance cosmetic formulation, both showed an improvement in DLQI ($p<0.05$).[40] The Sabgh formulation was slightly better than the Exuviance cosmetic formulation, but the difference was not statistically significant. There is low quality evidence from one non-randomized comparative study (n=144) showing that one-to-one skin camouflage lessons showed an improvement in DLQI scores compared with patients who did not receive one-to-one skin camouflage lessons ($p<0.05$). These patients were not randomized to treatment and the control group represented a very small subgroup (11 out of 155), who declined treatment and may have had very different baseline characteristics.[45] In a prospective case series (n=62) patients receiving a camouflage sample matching their skin complexion were followed up after at least 1 month and DLQI scores improved after camouflage use ($p<0.05$).[199] Another prospective case series (n=6) showed that children receiving camouflage therapy workshop along with a family member had a non-significant improvement in cDLQI scores 2 weeks after the workshop. There were only three cases of vitiligo included in the study and these were all female patients with segmental facial vitiligo, representing a specific subgroup of vitiligo patients.[137] A retrospective case series (n=20) showed that patients using dihydroxyacetone (DHA) for skin camouflage were dissatisfied with the product due to irregular brownish staining and no staining at all.[138] One study (n=854) online survey was used to estimate the QoL of Chinese vitiligo patients using skin camouflage for > 1 month [median 50 months; range (1 -216)] [166]. The mean (SD) DLQI score was 5.83 (5.75) signifying a small – moderate effect on the patients' QoL. The mean DLQI scores were highest for three domains: daily activities, leisure, and, symptoms and feelings. "Very much" patient satisfaction with camouflage therapy us achieved in 82/854 (9.3%) patients. The DLQI score was shown to be independent of age, gender, marriage status, occupational status, anogenital involvement, patient perceived severity, symptoms (e.g. itching, pain, sunburn and koebner phenomenon), total cost and degree of satisfaction ($p< 0.05$).

Recommendation ↑: Consider a skin camouflage consultation in people with vitiligo who would like to explore this option.

Complementary therapies

There was very limited evidence identified for complementary therapy use in patients with vitiligo.

The Cochrane systematic review identified one double blind, randomised, placebo controlled small study, which showed Ginkgo Biloba (40 mg orally three times daily) was more effective compared with placebo at achieving ≥75% repigmentation ($p<0.05$).[200] Other complementary therapies identified in this review included pseudocatalase, catalase/dismutase superoxide and tetrahydrocurcuminoid cream, however the results were not reported in a way that would allow analysis of ≥ 75% repigmentation.

A meta-analysis identified showed a superior effectiveness ($p<0.00001$) of Chinese Herbal Medicine (CHM) in combination with NB-UVB compared to NB-UVB alone in achieving ≥50% repigmentation, however this was based on five RCTs, each investigating a different formulation of CHM; the heterogeneity makes drawing any conclusions difficult.[7] Another systematic review included trials of poor quality, most studies were poorly reported, often lacking information about dosing frequency, dosage strength, participant withdrawal, statistical analyses, and randomisation.[8] This poor quality makes it difficult to draw any conclusions.

Ten further studies were identified from our search.[38,49,50,73,123,139-142,164]

Two randomized controlled trials[49,50,73] and one non-randomized comparative study[38] were identified. Combination treatment of Vitamin E (one capsule of 400 UI orally daily)NB-UVB, and Khellin ointment 4% was shown to be more effective than vitamin E alone at achieving > 50% [RR=14.00 (95% CI 2.08 – 94.24), p=0.007] and > 75% repigmentation [RR=19.00 (95% CI 1.20 – 301.16, p=0.004].[38] Oral compound glycyrrhizin in combination with NB-UVB showed an improvement ($p<0.005$) in DLQI score compared with oral compound glycyrrhizin alone.[50]

Vitilinex lotion/emollient (consisting of herbal bio-actives with anti-oxidant properties) in combination with NB-UVB was shown to be more effective than Vitilinex monotherapy in achieving > 50% repigmentation [RR=1.94 (95% CI 1.27 – 2.97, p =0.002)] and >75% repigmentation [RR=2.59 (95% CI 1.38 – 4.87), p=0.003].[73] Similarly, vitilinex in combination with NB-UVB was shownt to be more effective at achieving >50% and >75% repigmentation, however, this was not a statistically significant result. [73]

Six of the eleven studies were non-comparative.[139-142,164,165] One non-comparative study (n=436) investigated climatotherapy involving dead sea bathing and sunshine exposure, this was associated with >50% repigmentation in only 3.9% of 436 patients.[139] A study (n=20) investigating the effect of leech application weekly for 6 months in 20 patients reported >50% repigmentation in 9 of 20 patients and >75% repigmentation in 2 of 20.[140] A further non-comparative study (n=42) of Vitalog (containing 80 mg of Stachytarpheta cayensensis Vahl aqueous dried extract) reported 69 of 99 lesions achieving ≥75% repigmentation.[141] Nigella seed oil applied to the hands, face, and genital regions twice daily for 6 month was shown to be effective at achieving ≥ 50% repigmentation, but this was based on a small sample size (47 patches). [164] Autologous non-cultured epidermal cell suspension combined with platelet rich fibrin was also shown to be effective at achiving ≥ 50% repigmentation, but this was also based on a very small sample size (n=7).[165]

One non-comparative study (case series) reported on the use of eight different homeopathic compounds over 24 months, 140 of 200 patients achieved 100% repigmentation;[142] 69% of the study population were less than 20 years old, this may be an indicator of the natural history of the disease.

Whilst vitamin E, antioxidant pool, and Ginkgo Biloba were shown to be statistically significantly effective at improving repigmentation, the GDG felt there was insufficient high-quality evidence to make recommendations for these intereventions.

Θ There is insufficient evidence to recommend a specific complementary therapy for people with vitiligo.

Certainty of evidence

TOPICAL THERAPY

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	Betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream	Tacrolimus 0.1% ointment vs. placebo	None	CO_2 laser + topical 5FU vs. topical 5FU
	Betamethasone dipropionate 0.05% cream + calcipotriene	[†]Topical cream (Photocil) + natural sunlight exposure vs.		Topical 5FU vs. CO_2 laser

	0.005% ointment vs. calcipotriene 0.005% ointment	placebo cream + natural sunlight exposure		
	Betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment			
	PUVA + calcipotriol vs. calcipotriol			
	Re-pigmenta vs. Bioskin			
	Re-pigmenta + Bioskin vs. Re-pigmenta			
	Re-pigmenta vs. Clobetasol 0.05%			
	Re-pigmenta + Bioskin vs. Bioskin			
	Bioskin vs. clobetasol 0.05% propionate	Tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%		
	Re-pigmenta + Bioskin vs. clobetasol propionate 0.05%	Hand-held NB-UVB + mometasone furoate 0.1% vs. mometasone furoate 0.1%		
	Tacrolimus 0.1% + topical pseudocatalase/superoxide diutase gel vs. tacrolimus 0.1%			
	Tacrolimus 0.03% vs. pimecrolimus 1%			

† Based on important outcomes – no raw data or quality rating for critical outcomes

SYSTEMIC THERAPY

	Certainty of evidence			
Interv	**Very low**	**Low**	**Moderate**	**High**
	Oral methotrexate (MTX) vs. OMP (betamethasone/dexamethasone)	Minocycline 100mg/day vs. (OMP) 2.5mg dexamethasone	None	None

	Mel + khel + vitamin E vs. Vitamin E			

LASER AND LIGHT THERAPY

	Certainty of evidence			
	Very low	**Low**	**Moderate**	**High**
Interventions	home-based hand-held phototherapy vs. institution-based excimer lamp	NB-UVB + Vitamin E vs. NB-UVB	CO_2 laser vs. Topical 5FU	Topical 5FU + CO_2 laser vs. CO_2 laser
		Home-based hand-held NB-UVB treatment vs. placebo	Afamelanotide + NB-UVB vs. NB-UVB	
		[†]NB-UVB vs. PUVA		Yiqiqubai granule + 308nm excimer laser vs. 308 nm excimer laser
	Bioskin vs. tacrolimus 0.1% + Bioskin	Tacrolimus 0.1% + excimer laser vs. excimer laser		
	Bioskin vs. pimecrolimus 1% + Bioskin	Home-based hand-held NB-UVB vs. topical mometasone furorate 0.1%		Yiqiqubai granule + 308nm excimer laser vs. yiqiubai granule
	Microneedling + NB-UVB + topical triamcinolone vs. NB-UVB			
	Apremilast + NB-UVB vs. placebo + NB-UVB		Halometasone + excimer laser vs. excimer laser	PRP + excimer laser vs. excimer laser
			Home-based NB-UVB vs. hospital-based NB-UVB	
	Pimecrolimus 1% + excimer laser vs. excimer laser			
			Vitilinex + NB-UVB vs. NB-UVB	

	Home-based NB-UVB vs. outpatient NB-UVB			
	Home-based hand-held NB-UVB + TCS vs. hand-held NB-UVB			

† Based on important outcomes – no raw data or quality rating for critical outcomes

COMBINATION THERAPY

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%	punch grafting + corticosteroids vs. punch grafting + PUVA	None	None
	alpha lipoic acid + betamethasone injection + NB-UVB (combination) vs. placebo + betamethasone injection + NB-UVB (control)	Excimer laser + tacrolimus 0.1% vs. excimer laser + halometasone		
	MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%			
	MEL + khellin 4% + tacrolimus 0.1% vs. MEL			
	MEL + tacrolimus 0.1% vs. MEL + khellin 4%			
	MEL + tacrolimus 0.1% vs. MEL			
	MEL + khellin 4% vs. MEL			

	Tacrolimus 0.1% + excimer laser vs. pimecrolimus 1% + excimer laser			

SURGICAL THERAPY

	Certainty of evidence			
	Very low	**Low**	**Moderate**	**High**
Interventions	Ultra-thin skin grafting vs. miniature punch grafting	Microneedling + tacrolimus 0.1% vs. microneedling	NCES Blister roof graft vs. NCES Thiersch graft	Non-cultured epidermal cell suspension/non-cultured dermal cell suspension vs. non-cultured cell suspension
	Ultra-thin skin grafting vs. non-cultured epidermal cell suspension			
	Non-cultured epidermal cell suspension vs. miniature punch grafting			
	Cold trypsinization preparation non-cultured epidermal cell suspension vs. warm trypsinization preparation non-cultured epodermal cell			

	Microneedling + NB-UVB vs. microneedling + topical triamcinolone			
	Follicular unit extraction vs. pucking hair follicle			
	Non-cultured extracted hair follicle outer root sheath cell suspension vs. non-cultured cell suspension			

CAMOUFLAGE THERAPY

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	None	Sabgh (herbal formulation) vs. Exuviance (active ingredient is titanium dioxide)	None	None

COMPLEMENTARY THERAPY

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	CO_2 laser + platelet rich plasma vs. plalelet rich placma	None	Vitilinex (herbal bio-actives) + NB-UVB vs. vitilinex	None

			Oral compound glycyrrhizin + UVB vs. oral compound glycyrrhizin	
	Platelet rich plasma vs. CO_2			
	Monochromatic excimer light + khellin + vitamin E vs. vitamin E		yiqiqubai granule + 308 nm excimer laser vs. yiqiqubai granule	

DEPIGMENTATION

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	Facial depigmentation vs. extra-facial depigmentation	None	None	None

NON-COMPARATIVE STUDIES (VERY LOW CERTAINY EVIDENCE)

Topical therapies	Ruxolitinib 1.5%
	Ruxolitinib 1.5% cream + optional NB-UVB
Depigmentation therapies	Laser assisted depigmentation (QS laser)
	694-nm QSR laser
	Q-switched Nd:YAG laser at 532-nm wavelength
	Monobenzyl ether of hydroquinone (MBEH)

	Cryotherapy and/or 755nm laser therapy
Systemic therapies	Tofacitinib + NB-UVB
Combination therapies	Tacrolimus 0.03% or tacrolimus 0.1% with NB-UVB
	Minigraft + phototherapy
	Nutritional therapy + topical therapy
	Nutritional therapy + systemic steroid pulse therapy or triamcinolone intralesional injection
	Nutritional therapy + excimer laser
	Nutritional therapy + topical therapy + systemic steroid pulse therapy or triamcinolone intralesional injection
	Nutritional therapy + topical therapy + excimer laser
	Nutritional therapy + systemic steroid pulse therapy or triamcinolone intralesional injection + excimer laser
	Nutritional therapy + topical therapy + systemic steroid pulse therapy or triamcinolone intralesional injection + excimer laser
	Nutritional therapy + epidermal graft
	Methyl prednisolone + NB-UVB
	Methyl prednisolone + topical 0.01% fluticasone ointment
Surgical therapies	Autologous epidermal transplantation
	Melanocyte-keratinocyte transplantation
	Motorized 0.8-mm micro-punch grafting
	Topical flurouracil 5% needling (26-G needle)
Skin camouflage therapies	Skin camouflage
	Dihydroxyacetone (DHA) 6%
	Camouflage therapy workshop
	Skin camouflage
Complementary therapies	Dead sea climatotherapy
	Leeches

	Vitalog (containing 80 mg of *Stachytarpheta cayensensis Vahl* aqueous dried extract)
	Homeopathy
	Nigella satvia seed oil
	Autologous NCES combined with platelet rich fibrin (PRF)

Patient values and preferences	Patients with vitiligo generally do not report physical symptoms as a result of the loss of their pigment but the change in their appearance, the unpredictable progression of the condition contribute in some patients to emotional stress and psychosocial burden. Currently there is no 'cure' for vitiligo, but patients are encouraged by newly emerging oral and topical treatments. Patients are hopeful that a more effective and long-term treatment option will be available to them in the next decade. The following are views, reports, and recommendations, gained from patients' perspectives. These patients' perspectives have been provided from canvassing patients' views in the membership of Vitiligo Support UK and from our patient representatives: **<u>Gaining access to a diagnosis and treatment</u>** Patients report increasing difficulties in accessing treatment in both in primary and secondary care.

	It is important to explain clearly to your General Practitioner or dermatologist the extent to which your vitiligo is affecting you and your daily work and life, to gain access to a referral or a treatment pathway. Patients' experiences are that, if you are seeking treatment, it is useful to photograph your vitiligo and monitor its progression over a period of 1-3 months. This can provide a clear picture to your GP or dermatologist as to how quickly it is developing. There is a link between thyroid disease and vitiligo. Patients need to be aware of symptoms and their family history of thyroid disease as well as other autoimmune conditions such as pernicious anemia, Addison's disease, atopic dermatitis, and Type I diabetes amongst others. In vitiligo patients, extensive blood tests are usually not required. There is no specific blood test to diagnose vitiligo. If patients are concerned about their risk of autommine diseases or a possible Vitamin D deficiency because of a reduction in their 'incidental exposure' to sun or frequent usage of sunscreen when outdoors, it is recommended that patients discuss this with their GP. The advice of Public Health England is that everyone should supplement with Vitamin D between the months of October to April (https://www.gov.uk/government/news/phe-publishes-new-advice-on-vitamin-d) **Standard Treatments** The first-line treatment, which is usually offered to vitiligo patients by their GP, is a high potency steroid cream. Topical immunomodulators such as tacrolimus and pimecrolimus are often being prescribed by dermatologists only (secondary care). Patients often feel that they have to persist in order to get access to secondary care and especially to hospital phototherapy units. Many patients opt for home hand-held or full-body phototherapy devices, as they become increasingly available online. The risks of using these devices unmonitored include phototherapy-associated side effects such as burns, especially of sensitive areas (eyelids and genitals), and skin cancer. It is recommended that patients follow carefully the information leaflet provided by the device's manufacturer and consult their dermatologist. **Covering up your vitiligo**

	Traditionally, cosmetic camouflage has been the main way of covering up vitiligo patches. The products are gender-neutral and have to be applied on a daily basis. Cosmetic camouflage face-to-face tutorials are available through the charity "Changing Faces". Appointments can either be made online via the Changing Faces https://www.changingfaces.org.uk/skin-camouflage/what-is-the-skin-camouflage-service) or through a referral from a GP or a dermatologist. Other products can also provide a good and long-lasting alternative to covering up if you chose not to use camouflage, and support groups will be able to direct patients further as to which are recommended by users. **Sunscreen** Many vitiligo patients report that their vitiliginous patches burn easily when exposed to sunlight. It is strongy recommended that sunscreen with four-star UV rating and factor 50 SPF need to be applied on vitiligo patches, before leaving going outdoors into the sun. It is important to remember to reapply sunscreen throughout the day and particularly after swimming or sweating heavily and to recognise the limited amount of time you can spend in the sun before sustaining burns on your vitiligo patches. Use shade, clothing and hats, and time out of the sun to reduce your risk. Sunscreens are sometimes available on prescitption for vitiligo patients; however, many Clinical Commissioning Groups have removed sunscreens from their list of prescribable items.
Cost	One systematic review was identified, which aimed to ascertain all economic evidence relating to vitiligo.[201] The systematic review identified only two studies with an economic objective, one study conducted a willingness-to-pay survey in 3319 German vitiligo patients; 1023 of 3319 patients responded and 32.5% stated that they would be willing to make a one-off investment of ≥ €5000[202] and the second study used routinely collected data to estimate the annual direct health-care burden cost of treating vitiligo, which was $175 000 000 in 2004.[203] However, both studies did not conduct a full economic evaluation of vitiligo treatments from any perspective (patient, hospital/clinic, healthcare system or society),[202,203] this highlights the lack of cost-effectivness studies for interventions used in vitiligo. **Future Research Recommendation:** A cost-effectiveness analysis of treatments for people with vitiligo within a U.K. healthcare setting.

Other considerations	The GDG agreed on the importance of guidance for the treatment of common mental health conditions and recognition of depression in people with long-term conditions such as vitiligo. The following NICE guidance may be helpful when considering the mental health of people with vitiligo: • Common mental health problems: identification and pathway to care [CG123][204] • Depression in adults: recognition and management [CG90][205] • Depression in adults with a chronic physical health problem: recognition and management [CG91][206] The following tools can be used when assessing a person with a suspected mental health disorder: • The 4-item health questionnaire (PHQ-4) Patient Health Questionnaire-4 (PHQ-4) | QxMD • The 9-item health questionnaire (PHQ-9) https://patient.info/doctor/patient-health-questionnaire-phq-9 • 2-item Gerneralised Anxiety Disorder Scale (GAD-2) Generalized Anxiety Disorder 2-item (GAD-2) - Mental Disorders Screening - National HIV Curriculum (uw.edu) • 7-item Generalised Anxiety Disorder Scale (GAD-7) https://patient.info/doctor/generalised-anxiety-disorder-assessment-gad-7 The following tools for assessing QoL are specific for people with vitiligo: • Vitiligo Specific health related Quality of Life Instrument (VitiQoL)[207] • Vitiligo Impact Patient Scale (VIPs)[198] The GDG formulated the following general recommendations for diagnosis and management of people with vitiligo based on practice: **Recommendation GPP:** Undertake a full history for people with vitiligo including the site and type of vitiligo (segmental, non-segmental), disease extent (affected body surface area), disease stability, speed of onset, trigger factors, quality of life, psychological/psychosocial impact, and personal and family history of associated thyroid dysfunction or other autoimmune disease.

	Recommednation GPP: Screen for anti-thyroid antibodies and thyroid function in people with vitiligo (including children) to identify those at high risk of developing autoimmune thyroid disease. **Recommendation GPP:** Discuss with people with vitiligo (including children) the psychosocial impact of living with the condition, emphasizing the relationship between the skin and the mind. **Recommednation GPP:** Refer people with suspected vitiligo to a healthcare professional experienced in managing the condition (secondary care specialist or general physicians with enhanced role, GPwER) if: • the condition is progressing rapidly • there is diagnostic uncertainty • the condition has a significant psychosocial impact • the condition is not responding to topical treatment. **Recommendation ↑↑:** Assess* and monitor the QoL and level of psychological distress associated with living with vitiligo. Assessment tools that can be used include Patient Health Questionnaire 4 (PHQ4)[208], Patient Health Questionnaire 9 (PHQ9)[209], Generalized Anxiety Disorder 7 (GAD7)[210], Dermatology Life Quality Index (DLQI)[211], and more specifically the vitiligo impact patient scale (VIPs)[198] or Vitiligo specific quality of life (VitiQoL)[207]. **Recommendation GPP:** Provide people with vitiligo (including children) with a patient information leaflet on the condition and prescribed treatments (e.g. British Association of Dermatologists PILs www.skinhealthinfo.org.uk/a-z-conditions-treatments/). **Recommendation GPP:** Consider measuring serum vitamin D levels in people with vitiligo who are avoiding all sun exposure. If levels are reduced or deficient, advise that they may wish to consider taking supplementary vitamin D3 (10-25 micrograms per day) and increasing their intake of foods high in vitamin D, such as oily fish, eggs, meat, fortified margarines, and cereals. **Recommendation GPP:** Monitor the skin of people with vitiligo for treatment response (or rapid progression) via medical photography (digital imaging) taken at the beginning of treatment and at regular intervals of approximately 3-6 months. Alternatively, body surface area (BSA) and area affected by vitiligo should be documented or patients could use

		personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com. **Recommendation GPP:** Offer sunscreen with 4* or 5* UVA rating and SPF 50 to people with vitiligo, applied to affected patches and surrounding skin before going outdoors into the sun.
LIST OF RECOMMENDATIONS		
GENERAL RECOMMENDATIONS		
R1	**GPP**	Undertake a full history for people with vitiligo including the site and type of vitiligo (**segmental, non-segmental**), disease extent (affected body surface area), disease stability, speed of onset, trigger factors, quality of life, psychological/psychosocial impact, and personal and family history of associated thyroid dysfunction or other autoimmune disease.
R2	**GPP**	Screen for anti-thyroid antibodies and thyroid function in people with vitiligo (including children) to identify those at high risk of developing autoimmune thyroid disease.
R3	**GPP**	Discuss with people with vitiligo (including children) the psychosocial impact of living with the condition, emphasizing the relationship between the skin and the mind.
R4	**GPP**	Refer people with suspected vitiligo to a healthcare professional experienced in managing the condition (secondary care specialist or general physicians with enhanced role, GPwER) if: • the condition is progressing rapidly • there is diagnostic uncertainty • the condition has a significant psychosocial impact • the condition is not responding to topical treatment.
R5	**↑↑**	Assess* and monitor the QoL and level of psychological distress associated with living with vitiligo. Assessment tools that can be used include Patient Health Questionaire 4 (PHQ4),[208]Patient Health Questionnaire 9 (PHQ9),[209] Generalized Anxiety Disorder 7

		(GAD7),[210] Dermatology Life Quality Index (DLQI),[211] and more specifically the vitiligo impact patient scale (VIPs)[198] or Vitiligo specific quality of life (VitiQoL).[207]
R6	**GPP**	Provide people with vitiligo (including children) with a patient information leaflet on the condition and prescribed treatments (e.g. British Association of Dermatologists PILs www.skinhealthinfo.org.uk/a-z-conditions-treatments/).
R7	**GPP**	Consider measuring serum vitamin D levels in people with vitiligo who are avoiding all sun exposure. If levels are reduced or deficient, advise that they may wish to consider taking supplementary vitamin D3 (10-25 micrograms per day) and increasing their intake of foods high in vitamin D, such as oily fish, eggs, meat, fortified margarines and cereals.
R8	**GPP**	Monitor the skin of people with vitiligo for treatment response (or rapid progression) via medical photography (digital imaging) taken at the beginning of treatment and at regular intervals of approximately 3-6 months. Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com.
R9	**GPP**	Offer sunscreen with 4* or 5* UVA rating and SPF 50 to people with vitiligo, applied to affected patches and surrounding skin before going outdoors into the sun.
TOPICAL THERAPIES		
R10	**↑↑**	Offer a potent or very potent topical corticosteroid once daily to minimize potential side effects to people with vitiligo as the first-line treatment in primary or secondary care, avoid periocular area.
R11	**GPP**	Discuss with people with vitiligo the amount of topical corticosteroids to be used, the site of application, and the safe use of a potent or very potent topical steroid when used correctly.
R12	**↑**	Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo as an alternative to potent or very potent topical corticosteroids.

R13	↑	Consider topical tacrolimus 0.1% ointment twice daily **under occlusion** on photo-exposed areas only in people with **non-facial vitiligo** as an alternative to potent or very potent topical corticosteroids.
R14	**GPP**	Consider an intermittent regimen of once daily application of potent or very potent topical corticosteroids with or without topical calcineurin inhibitors (more evidence for tacrolimus), factoring the risks and benefits, in people with vitiligo especially in areas with thinner skin, e.g. periocular region, genital area and skin flexures. Examples of intermittent regimens would include: • 1 week of potent or very potent corticosteroids and at least 1 week off • 1 week of potent or very potent topical corticosteroids alternating with ≥ 1 week of topical calcineurin inhibitor. Topical corticosteroids could be used for longer than 1 week in the intermittent regimen, after consideration of the risks and benefits.
R15	**GPP**	Reassess the use of topical treatments (**R10**-**R14**) every 3-6 months in people with vitiligo to check for improvement. The use of periodic medical photographs may help assess these changes.
Θ		There is insufficient evidence to recommend topical vitamin D analogues in people with vitiligo.
DEPIGMENTATION THERAPIES		
R16	**GPP**	Consider depigmentation therapies in people with **extensive vitiligo** on visible sites, in whom the condition is having a negative psychological impact. This should be done after adequate psychological assessment and/or intervention. Please refer to the supplementary information document for further details.
SYSTEMIC THERAPIES		
R17	↑	Consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg/month for a further 3 months in combination with NB-UVB in people with **rapidly progressive vitiligo** to arrest activity of the disease after careful consideration of risks and benefits. (see **R18**)
R18	**GPP**	Consider an equivalent dose of alternative oral corticosteroids in people with **rapidly progressive vitiligo** if betamethasone is not available.

R19	↓↓	Do not offer azathioprine in combination with PUVA (and NB-UVB) to people with vitiligo due to the risk of malignancy.
Θ		There is insufficient evidence to recommend any currently available systemic treatments as monotherapy for people with **stable vitiligo**. However, there is some evidence for their use in combination with other treatments for **rapidly progressive vitiligo** (See **R17 and R18**)
Θ		There is insufficient evidence to recommend minocycline, methotrexate or tofacitinib for people with vitiligo.
LIGHT AND LASER MONO- AND COMBINATION THERAPIES		
R20	↑↑	Offer NB-UVB (whole body or localised, e.g. home-based hand-held) as first-line phototherapy to people with vitiligo who have an inadequate response to topical therapy and/or with **extensive** or **progressive** disease. This may be combined with topical calcineurin inhibitor[†] (more evidence for tacrolimus) or potent topical corticosteroid, [‡] for localised sites. Counsel patients on the significant risk of loss of response upon treatment cessation. [†] Prior to combination NB-UVB and topical tacrolimus treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. A shared decision should be made with the person with vitiligo, taking into account other alternatives, the individual's personal and family history of skin cancer risk and the impact of the vitiligo. [‡] The evidence for potent topical corticosteroid is limited. Prior to this combination, consider the risk/benefit ratio of the prolonged use of potent topical corticosteroid.
R21	**GPP**	Inform people with vitiligo who are eligible for NB-UVB of the requirements (depending on local protocols: a pre-therapy assessment, medical photographs taken prior to and during follow-ups 3-6 months, two to three sessions weekly possible for up to 1 year), and the likely response depending on the affected anatomical site (e.g. the face and trunk usually achieve better repigmentation than acral sites). Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com.

R22	↑	Only consider PUVA/PUVAsol in adults with vitiligo if treatment with NB-UVB is unavailable or has been ineffective. [§] § For contraindications refer to BAD PUVA guidelines 2016
R23	↑	Consider excimer laser or light in people with **localised vitiligo** in combination with topical calcineurin inhibitors (more evidence for tacrolimus). Prior to treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.
R24	↑	Consider CO_2 laser in combination with 5-fluorouracil in adults with **non-segmental vitiligo** on **hands and feet** if other treatments have been ineffective (apply 5-fluorouracil once daily for 7 days per month for 5 months; CO_2 laser treatments once a month for 5 months). This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.
Θ		There is insufficient evidence to recommend combination treatment of potent or very potent topical steroid with NB-UVB plus CO_2 laser for people with vitiligo.
SURGICAL THERAPIES		
R25	↑	Consider cellular grafting, e.g. blister grafting or cell suspension, in people with **stable**, **segmental,** or **non-segmental** vitiligo that is unresponsive to other treatments, and who remain distressed by the condition. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.
Θ		There is insufficient evidence to recommend mini-punch grafting in people with vitiligo.
PSYCHOLOGICAL THERAPIES		
R26	↑↑	Offer* information on self-help (e.g. leaflets, books, websites, apps) to people with vitiligo with mild psychological distress.
R27	↑↑	Offer* referral to psychological services for group or/and individual cognitive behavioural therapy (CBT) to people with vitiligo with moderate-to-severe psychological distress.
SKIN CAMOUFLAGE THERAPIES		

R28	↑	Consider a skin camouflage consultation in people with vitiligo who would like to explore this option.
COMPLEMENTARY THERAPIES		
Θ		There is insufficient evidence to recommend a specific complementary therapy for people with vitiligo.
FUTURE RESEARCH RECOMMENDATIONS		
FRR1		A national registry for people with vitiligo undergoing systemic or light therapy to identify outcomes and safety.
FRR2		A prospective, randomized controlled trial evaluating the safety and efficacy of topical tacrolimus combined with NB-UVB compared with commonly used interventions.
FRR3		A prospective, randomized controlled trial evaluating the safety and efficacy of topical 5-fluorouracil compared with commonly used interventions in adults with vitiligo.
FRR4		Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of oral JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.
FRR5		Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of topical JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.
FRR6		Prospective, randomized controlled trials evaluating the safety and efficacy of CO_2 laser for vitiligo compared with commonly used interventions in adults with vitiligo.
FRR7		Prospective randomized controlled trials evaluating the safety and efficacy of afamelanotide compared with commonly used interventions in adults with vitiligo.
FRR8		Prospective randomized controlled trials evaluating the effectiveness of psychological interventions in people with vitiligo.
FRR9		A cost-effectiveness analysis of treatments for people with vitiligo within a U.K. healthcare setting.

Appendix D: GRADE evidence tables

Topical therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥75% in **lesions** on hands and feet at 6-month follow-up, CO_2 laser + topical 5FU vs. topical 5FU												
1	randomized trials	not serious	not applicable	not serious	not serious	none	476/955 (49.8%)	26/703 (3.7%)	**RR 13.48** (9.19 to 19.76)	**462 more per 1,000** (from 303 more to 694 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Complete repigmentation (100%) in **lesions** on hands and feet at 6-month follow-up, CO_2 laser + topical 5FU vs. topical 5FU												
1	randomized trials	not serious	not applicable	not serious	not serious	none	362/955 (37.9%)	15/703 (2.1%)	**RR 17.77** (10.70 to 29.50)	**358 more per 1,000** (from 207 more to 608 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥ 50% in **lesions** on hands and feet at 6-month follow-up, CO_2 laser + topical 5FU vs. topical 5FU												
1	randomized trials	not serious	not applicable	not serious	not serious	none	534/955 (55.9%)	40/703 (5.7%)	**RR 9.83** (7.24 to 13.35)	**502 more per 1,000** (from 355 more to 703 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Repigmentation ≥75% in lesions on hands and feet at 6-month follow-up, topical 5FU vs. CO_2 laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	26/703 (3.7%)	12/601 (2.0%)	**RR 1.85** (0.94 to 3.64)	**17 more per 1,000** (from 1 fewer to 53 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Complete repigmentation (100%) in lesions on hands and feet at 6-month follow-up, topical 5FU vs. CO_2 laser												
1	randomized trials	not serious	not applicable	not serious	not serious	none	15/703 (2.1%)	6/601 (1.0%)	**RR 2.14** (0.83 to 5.47)	**11 more per 1,000** (from 2 fewer to 45 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥ 50% in lesions on hands and feet at 6-month follow-up, topical 5FU vs. CO_2 laser												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	40/703 (5.7%)	20/601 (3.3%)	**RR 1.71** (1.01 to 2.89)	**24 more per 1,000** (from 0 fewer to 63 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Erythema in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	9/20 (45.0%)	7/20 (35.0%)	**RR 1.29** (0.60 to 2.77)	**102 more per 1,000** (from 140 fewer to 619 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Erythema in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/20 (15.0%)	3/20 (15.0%)	**RR 1.00** (0.23 to 4.37)	**0 fewer per 1,000** (from 115 fewer to 505 more)	⊕◯◯◯ VERY LOW	CRITICAL
Scaling in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/20 (10.0%)	5/20 (25.0%)	**RR 0.40** (0.09 to 1.83)	**150 fewer per 1,000** (from 208 more to 228 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Scaling in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	1/20 (5.0%)	**RR 1.00** (0.07 to 14.90)	**0 fewer per 1,000** (from 47 fewer to 695 more)	⊕◯◯◯ VERY LOW	CRITICAL
Dryness in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	7/20 (35.0%)	6/20 (30.0%)	**RR 1.17** (0.48 to 2.86)	**51 more per 1,000** (from 156 fewer to 558 more)	⨁⨁◯◯ LOW	CRITICAL
Dryness in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/20 (15.0%)	1/20 (5.0%)	**RR 3.00** (0.34 to 26.45)	**100 more per 1,000** (from 33 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate cream 0.05%												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/20 (10.0%)	3/20 (15.0%)	**RR 0.67** (0.12 to 3.57)	**49 fewer per 1,000** (from 132 fewer to 385 more)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical treatments	Control	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	1/20 (5.0%)	RR 1.00 (0.07 to 14.90)	0 fewer per 1,000 (from 47 fewer to 695 more)	⊕◯◯◯ VERY LOW	CRITICAL
Burning in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	8/20 (40.0%)	7/20 (35.0%)	**RR 1.14** (0.51 to 2.55)	**49 more per 1,000** (from 172 fewer to 542 more)	⊕◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	9/20 (45.0%)	6/20 (30.0%)	**RR 1.50** (0.66 to 3.43)	**150 more per 1,000** (from 102 fewer to 729 more)	⊕◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/20 (15.0%)	2/20 (10.0%)	**RR 1.50** (0.28 to 8.04)	**50 more per 1,000** (from 72 fewer to 704 more)	⨁◯◯◯ VERY LOW	CRITICAL
Scaling in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/20 (10.0%)	5/20 (25.0%)	**RR 0.40** (0.09 to 1.83)	**150 fewer per 1,000** (from 208 more to 228 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Scaling in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	0/20 (0.0%)	**RR 3.00** (0.13 to 69.52)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Dryness in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	7/20 (35.0%)	0/20 (0.0%)	**RR 15.00** (0.91 to 246.20)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Dryness in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/20 (15.0%)	0/20 (0.0%)	**RR 7.00** (0.38 to 127.32)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/20 (10.0%)	0/20 (0.0%)	**RR 5.00** (0.26 to 98.00)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	0/20 (0.0%)	**RR 3.00** (0.13 to 69.52)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Burning in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	8/20 (40.0%)	5/20 (25.0%)	**RR 1.60** (0.63 to 4.05)	**150 more per 1,000** (from 93 fewer to 763 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	7/20 (35.0%)	6/20 (30.0%)	**RR 1.17** (0.48 to 2.86)	**51 more per 1,000** (from 156 fewer to 558 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/20 (15.0%)	2/20 (10.0%)	**RR 1.50** (0.28 to 8.04)	**50 more per 1,000** (from 72 fewer to 704 more)	⨁◯◯◯ VERY LOW	CRITICAL
Scaling in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	5/20 (25.0%)	5/20 (25.0%)	**RR 1.00** (0.34 to 2.93)	**0 fewer per 1,000** (from 165 fewer to 483 more)	⨁◯◯◯ VERY LOW	CRITICAL
Scaling in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	0/20 (0.0%)	**RR 3.00** (0.13 to 69.52)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Dryness in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	6/20 (30.0%)	0/20 (0.0%)	**RR 13.00** (0.78 to 216.39)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Dryness in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	0/20 (0.0%)	**RR 3.00** (0.13 to 69.52)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/20 (15.0%)	0/20 (0.0%)	**RR 7.00** (0.38 to 127.32)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 5-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	0/20 (0.0%)	**RR 3.00** (0.13 to 69.52)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Burning in patients at 1-month follow-up, betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	7/20 (35.0%)	5/20 (25.0%)	**RR 1.40** (0.53 to 3.68)	**100 more per 1,000** (from 118 fewer to 670 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, PUVA + calcipotriol vs. calcipotriol												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	21/30 (70.0%)	0/30 (0#.0%)	**RR 43.00** (2.72 to 678.92)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Erythema in patients at 6-month follow-up, PUVA + calcipotriol vs. calcipotriol												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	4/30 (13.3%)	2/30 (6.7%)	**RR 2.00** (0.40 to 10.11)	**67 more per 1,000** (from 40 fewer to 607 more)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus and burning in patients at 6-month follow-up, PUVA + calcipotriol vs. calcipotriol												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	5/30 (16.7%)	3/30 (10.0%)	**RR 1.67** (0.44 to 6.36)	**67 more per 1,000** (from 56 fewer to 536 more)	⨁◯◯◯ VERY LOW	CRITICAL
Nausea and vomiting in patients at 6-month follow-up, PUVA + calcipotriol vs. calcipotriol												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/30 (10.0%)	0/30 (0.0%)	**RR 7.00** (0.38 to 129.93)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Participant reported treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9 mos., Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [b]	not applicable	not serious	serious [a]	none	34/175 (19.4%)	20/173 (11.6%)	**RR 1.68** (1.01 to 2.80)	**79 more per 1,000** (from 1 more to 208 more)	⨁⨁◯◯ LOW	CRITICAL
Repigmentation ≥75% at 9 mos. follow-up, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	not serious	none	18/175 (10.3%)	4/173 (2.3%)	**RR 4.45** (1.54 to 12.88)	**80 more per 1,000** (from 12 more to 275 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment-related adverse events at 9 mos., Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	not serious	none	52/175 (29.7%)	24/173 (13.9%)	**RR 2.14** (1.39 to 3.31)	**158 more per 1,000** (from 54 more to 320 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Erythema (Grade 3 and 4) at 9 mos. in adults, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [b]	not applicable	not serious	not serious	none	26/135 (19.3%)	2/133 (1.5%)	**RR 12.81** (3.10 to 52.89)	**178 more per 1,000** (from 32 more to 780 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Erythema (Grade 3 and 4) at 9 mos. in children, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	serious [a]	none	7/40 (17.5%)	1/40 (2.5%)	**RR 7.00** (0.90 to 54.32)	**150 more per 1,000** (from 2 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Skin thinning at 9 mos. in adults, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	very serious [a]	none	5/135 (3.7%)	5/133 (3.8%)	**RR 0.99** (0.29 to 3.32)	**0 fewer per 1,000** (from 27 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL
Skin thinning at 9 mos. in children, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [b]	not applicable	not serious	very serious [a]	none	0/40 (0.0%)	1/40 (2.5%)	**RR 0.33** (0.01 to 7.95)	**17 fewer per 1,000** (from 25 fewer to 174 more)	⨁◯◯◯ VERY LOW	CRITICAL
Change in CHU9D at 9 mos. in children, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	serious [a]	none	40	40	-	MD **0.01 lower** (0.47 lower to 0.44 higher)	⨁⨁◯◯ LOW	CRITICAL
Change in VitiQoL at 21 mos. follow-up in adults, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	very serious [a]	none	135	133	-	MD **1.4 higher** (6.21 lower to 9.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Change in Skindex 29 at 21 mos. follow-up in adults, Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [b]	not applicable	not serious	very serious [a]	none	135	133	-	MD **2.4 higher** (3.4 lower to 8.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Change in EQ-5D at 9 mos., Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	not serious	none	175	173	-	MD **0.06 higher** (0.02 higher to 0.1 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Participant reported loss of treatment response at 21 mos. follow-up in those with treatment success at 9 mos., Hand-held home-based NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomised trials	serious [b]	not applicable	not serious	very serious [a]	none	14/34 (41.2%)	6/20 (30.0%)	**RR 1.37** (0.63 to 3.00)	**111 more per 1,000** (from 111 fewer to 600 more)	⨁◯◯◯ VERY LOW	IMPORTANT
QoL of patients at 6-month follow-up using the DLQI, tacrolimus 0.1% ointment vs. placebo												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	19	16	-	MD **0.64 higher** (2.39 lower to 3.67 higher)	⨁⨁◯◯ LOW	CRITICAL
Maintenance of gained repigmentation in patients at 6-month follow-up, tacrolimus 0.1% ointment vs. placebo												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	17/19 (89.5%)	10/16 (62.5%)	**RR 1.43** (0.95 to 2.16)	**269 more per 1,000** (from 31 fewer to 725 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥ 50% in patients at 3-month follow-up, topical cream (Photocil) + natural sunlight exposure vs. placebo cream + natural sunlight exposure												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	4/7 (57.1%)	0/8 (0.0%)	**RR 10.13** (0.64 to 160.32)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Re-pigmenta vs. Bioskin												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	14/37 (37.8%)	26/43 (60.5%)	**RR 0.63** (0.39 to 1.01)	**224 fewer per 1,000** (from 6 more to 369 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Re-pigmenta vs. Bioskin												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	23/37 (62.2%)	35/43 (81.4%)	**RR 0.76** (0.57 to 1.02)	**195 fewer per 1,000** (from 16 more to 350 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Re-pigmenta + Bioskin vs. Re-pigmenta												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	26/36 (72.2%)	14/37 (37.8%)	**RR 1.91** (1.20 to 3.02)	**344 more per 1,000** (from 76 more to 764 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Re-pigmenta + Bioskin vs. Re-pigmenta												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	32/36 (88.9%)	23/37 (62.2%)	**RR 1.43** (1.08 to 1.89)	**267 more per 1,000** (from 50 more to 553 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Re-pigmenta vs. clobetasol propionate 0.05%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	14/37 (37.8%)	19/33 (57.6%)	**RR 0.66** (0.40 to 1.09)	**196 fewer per 1,000** (from 52 more to 345 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Re-pigmenta vs. clobetasol propionate 0.05%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	23/37 (62.2%)	27/33 (81.8%)	**RR 0.76** (0.56 to 1.02)	**196 fewer per 1,000** (from 16 more to 360 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Re-pigmenta + Bioskin vs. Bioskin												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	26/36 (72.2%)	26/43 (60.5%)	**RR 1.19** (0.87 to 1.64)	**115 more per 1,000** (from 79 fewer to 387 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Re-pigmenta + Bioskin vs. Bioskin												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	32/36 (88.9%)	35/43 (81.4%)	**RR 1.09** (0.91 to 1.31)	**73 more per 1,000** (from 73 fewer to 252 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Bioskin vs. clobetasol 0.05% propionate												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	26/43 (60.5%)	19/33 (57.6%)	**RR 1.05** (0.72 to 1.54)	**29 more per 1,000** (from 161 fewer to 311 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Bioskin vs. clobetasol 0.05% propionate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	not serious	none	35/43 (81.4%)	27/33 (81.8%)	**RR 0.99** (0.80 to 1.23)	**8 fewer per 1,000** (from 164 fewer to 188 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Re-pigmenta + Bioskin vs. clobetasol propionate 0.05%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	26/36 (72.2%)	19/33 (57.6%)	**RR 1.25** (0.88 to 1.79)	**144 more per 1,000** (from 69 fewer to 455 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Re-pigmenta + Bioskin vs. clobetasol propionate 0.05%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	32/36 (88.9%)	27/33 (81.8%)	**RR 1.09** (0.89 to 1.32)	**74 more per 1,000** (from 90 fewer to 262 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, betamethasone valerate 0.1% + oral simvastatin 40mg vs. betamethasone valerate 0.1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	16/44 (36.4%)	12/44 (27.3%)	**RR 1.33** (0.72 to 2.48)	**90 more per 1,000** (from 76 fewer to 404 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, tacrolimus 0.03% vs. clobetasol 0.05%												
1	Randomized trials	serious [b]	not applicable	not serious	serious [a]	none	1/30 (3.3%)	9/30 (30.0%)	**RR 0.11** (0.01 to 0.82)	**267 fewer per 1,000** (from 54 fewer to 297 fewer)	⨁⨁◯◯ LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, tacrolimus 0.03% vs. clobetasol 0.05%												
1	Randomized trials	serious [b]	not applicable	not serious	not serious [a]	none	3/30 (10.0%)	14/30 (46.7%)	**RR 0.21** (0.07 to 0.67)	**369 fewer per 1,000** (from 154 fewer to 434 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥50% in patients at 3-month follow-up, tacrolimus 0.03% vs. betamethasone valerate 0.1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	very serious [b]	not applicable	not serious	very serious [a]	none	25/33 (75.8%)	28/33 (84.8%)	**RR 0.89** (0.70 to 1.14)	**93 fewer per 1,000** (from 119 more to 255 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 9-month follow-up, tacrolimus 0.1% + topical pseudocatalse/superoxide dimutase gel vs. tacrolimus 0.1% gel												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/25 (8.0%)	1/24 (4.2%)	**RR 1.92** (0.19 to 19.82)	**38 more per 1,000** (from 34 fewer to 784 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 9-month follow-up, tacrolimus 0.1% + topical pseudocatalse/superoxide dimutase gel vs. tacrolimus 0.1% gel												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	9/25 (36.0%)	6/24 (25.0%)	**RR 1.44** (0.60 to 3.43)	**110 more per 1,000** (from 100 fewer to 608 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥ 75% (> 75%) in patients at 3-month post-treatment follow-up, tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	Randomized trials	serious [b]	not serious	not serious	not serious	none	32/54 (59.3%)	17/54 (31.5%)	**RR 1.88** (1.20 to 2.95)	**277 more per 1,000** (from 63 more to 614 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain in patients at 3-month follow-up, tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%												
2	Randomized trials	serious [b]	not serious	not serious	not serious	none	18/54 (33.3%)	0/54 (0.0%)	**RR 19.00** (2.63 to 137.02)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Itching in patients at 3-month post-treatment follow-up, tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%												
2	Randomized trials	serious [b]	serious[c]	not serious	very serious [a]	none	10/54 (18.5%)	16/54 (29.6%)	**RR 0.64** (0.32 to 1.27)	**107 fewer per 1,000** (from 201 fewer to 80 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 3-month post-treatment follow-up, tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	7/30 (23.3%)	8/30 (26.7%)	**RR 0.88** (0.36 to 2.11)	**32 fewer per 1,000** (from 171 fewer to 296 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% (>50%) in patients at 3-month follow-up, tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%												
2	Randomized trials	serious [b]	not serious	not serious	not serious	none	40/54 (74.1%)	20/54 (37.0%)	**RR 2.00** (1.37 to 2.93)	**370 more per 1,000** (from 137 more to 715 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥ 75% (>75%) at 6-month follow-up in infants (< 2 years) with vitiligo, tacrolimus 0.03% vs. pimecrolimus 1%												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	8/23 (34.8%)	6/23 (26.1%)	**RR 1.33** (0.55 to 3.24)	**86 more per 1,000** (from 117 fewer to 584 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mild redness and scratch in infants (<2 years) with vitiligo at 6-month follow-up, tacrolimus 0.03% vs. pimecrolimus 1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	3/23 (13.0%)	2/23 (8.7%)	**RR 1.50** (0.28 to 8.16)	**43 more per 1,000** (from 63 fewer to 623 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% (>50%) in infants (<2 years) with vitiligo at 6-month follow-up, tacrolimus 0.03% vs. pimecrolimus 1%												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	16/23 (69.6%)	15/23 (65.2%)	**RR 1.07** (0.71 to 1.60)	**46 more per 1,000** (from 189 fewer to 391 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥ 50% (>50%) in patients at 12-month follow-up, bFGF related decapeptide solution + tacrolimus 0.1% vs. tacrolimus 0.1%												
1	Randomized trials	serious [b]	not applicable	not serious	serious [a]	none	9/40 (22.5%)	3/44 (6.8%)	**RR 3.30** (0.96 to 11.34)	**157 more per 1,000** (from 3 fewer to 705 more)	⨁⨁◯◯ LOW	IMPORTANT

Abbreviations: CI, Confidence interval; **RR,** Risk ratio; **MD,** Mean difference

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Large variation in point estimates, little overlap in confidence intervals and a high statistically significant I^2 value

Systemic therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Systemic treatments	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, minocycline 100mg/day vs. oral minipulse (OMP) 2.5mg dexamethasone												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	3/25 (12.0%)	1/25 (4.0%)	**RR 3.00** (0.33 to 26.92)	**80 more per 1,000** (from 27 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse effects in patients at 6-month follow-up, minocycline 100mg/day vs. OMP 2.5mg dexamethasone												
1	randomized trials	not serious	not applicable	not serious	very serious [b]	none	5/25 (20.0%)	7/25 (28.0%)	**RR 0.71** (0.26 to 1.95)	**81 fewer per 1,000** (from 207 fewer to 266 more)	⨁⨁◯◯ LOW	CRITICAL
Patients without new lesions at 6-month follow-up, minocycline 100mg/day vs. OMP 2.5mg dexamethasone												
1	randomized trials	not serious	not applicable	not serious	serious [b]	none	19/25 (76.0%)	22/25 (88.0%)	**RR 0.86** (0.66 to 1.12)	**123 fewer per 1,000** (from 106 more to 299 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Systemic treatments**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse effects in patients at 6-month follow-up, oral methotrexate (MTX) vs. OMP (betamethasone/dexamethasone)												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	4/26 (15.4%)	5/26 (19.2%)	**RR 0.80** (0.24 to 2.65)	**38 fewer per 1,000** (from 146 fewer to 317 more)	⨁◯◯◯ VERY LOW	CRITICAL

Abbreviations: CI: Confidence interval; **RR:** Risk ratio

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Light and laser therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥75% in lesions on hands and feet at 6-month follow-up, topical 5FU + CO_2 laser vs. CO_2 laser												
1	randomized trials	not serious	not applicable	not serious	not serious	none	476/955 (49.8%)	12/601 (2.0%)	**RR 24.96** (14.21 to 43.86)	**478 more per 1,000** (from 264 more to 856 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete repigmentation (100%) in lesions on hands and feet at 6-month follow-up, topical 5FU + CO_2 laser vs. CO_2 laser												
1	randomized trials	not serious	not applicable	not serious	not serious	none	362/955 (37.9%)	6/601 (1.0%)	**RR 37.97** (17.06 to 84.52)	**369 more per 1,000** (from 160 more to 834 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Repigmentation ≥50% in lesions on hands and feet at 6-month follow-up, topical 5FU + CO_2 laser vs. CO_2 laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	not serious	none	534/955 (55.9%)	20/601 (3.3%)	**RR 16.80** (10.88 to 25.95)	**526 more per 1,000** (from 329 more to 830 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Repigmentation ≥75% in lesions on hands and feet at 6-month follow-up, CO_2 laser vs. Topical 5FU												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	12/601 (2.0%)	26/703 (3.7%)	**RR 0.54** (0.27 to 1.06)	**17 fewer per 1,000** (from 2 more to 27 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Complete repigmentation (100%) in lesions on hands and feet at 6-month follow-up, CO_2 laser vs. Topical 5FU												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	6/601 (1.0%)	15/703 (2.1%)	**RR 0.47** (0.18 to 1.20)	**11 fewer per 1,000** (from 4 more to 17 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥50% in lesions on hands and feet at 6-month follow-up, CO_2 laser vs. Topical 5FU												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	20/601 (3.3%)	40/703 (5.7%)	**RR 0.58** (0.35 to 0.99)	**24 fewer per 1,000** (from 1 fewer to 37 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, NB-UVB vs. PUVA												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	13/25 (52.0%)	8/25 (32.0%)	**RR 1.63** (0.82 to 3.22)	**202 more per 1,000** (from 58 fewer to 710 more)	⊕⊕◯◯ LOW	IMPORTANT
Mild erythema in patients at 6-month follow-up, NB-UVB + Vitamin E vs. NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	8/12 (66.7%)	8/12 (66.7%)	**RR 1.00** (0.57 to 1.76)	**0 fewer per 1,000** (from 287 fewer to 507 more)	⊕⊕◯◯ LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, NB-UVB + Vitamin E vs. NB-UVB												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	8/12 (66.7%)	5/12 (41.7%)	**RR 1.60** (0.73 to 3.49)	**250 more per 1,000** (from 113 fewer to 1000 more)	⊕⊕◯◯ LOW	IMPORTANT
Treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9 mos., hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
[1]	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	34/175 (19.4%)	27/169 (16.0%)	**RR 1.22** (0.77 to 1.92)	**35 more per 1,000** (from 37 fewer to 147 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥75% at 9 months follow-up, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
[1]	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	18/175 (10.3%)	9/169 (5.3%)	**RR 1.93** (0.89 to 4.18)	**50 more per 1,000** (from 6 fewer to 169 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment-related adverse events, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
[1]	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	52/175 (29.7%)	48/169 (28.4%)	**RR 1.05** (0.75 to 1.46)	**14 more per 1,000** (from 71 fewer to 131 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema (Grade 3 and 4) at 9 months follow-up in adults, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
[1]	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	26/135 (19.3%)	20/130 (15.4%)	**RR 1.25** (0.74 to 2.13)	**38 more per 1,000** (from 40 fewer to 174 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema (Grade 3 and 4) at 9 months follow-up in children, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
[1]	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	7/40 (17.5%)	6/39 (15.4%)	**RR 1.14** (0.42 to 3.08)	**22 more per 1,000** (from 89 fewer to 320 more)	⨁◯◯◯ VERY LOW	CRITICAL
Skin thinning at 9 months follow-up in adults, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
[1]	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	5/135 (3.7%)	2/130 (1.5%)	**RR 2.41** (0.48 to 12.19)	**22 more per 1,000** (from 8 fewer to 172 more)	⨁◯◯◯ VERY LOW	CRITICAL
Skin thinning at 9 months follow-up in children, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	7/40 (17.5%)	6/39 (15.4%)	**RR 1.14** (0.42 to 3.08)	**22 more per 1,000** (from 89 fewer to 320 more)	⨁◯◯◯ VERY LOW	CRITICAL
Change in CHU9D at 9 months in children, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	40	40	-	MD **0.01 lower** (0.46 lower to 0.45 higher)	⨁⨁◯◯ LOW	CRITICAL
Change in VitiQoL at 21 months follow-up in adults, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	135	130	-	MD **0.6 higher** (7.36 lower to 8.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Change in Skindex 29 at 21 months follow-up in adults, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	135	130	-	MD **4.4 higher** (1.72 lower to 10.52 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Change in EQ-5D in patients at 9 months, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	175	169	-	MD **0.01 lower** (0.06 lower to 0.04 higher)	⊕⊕◯◯ LOW	CRITICAL
Participant reported loss of treatment response at 21 months follow-up in those with treatment success at 9 months, hand-held NB-UVB + topical corticosteroid (mometasone furoate 0.1%) vs. hand-held NB-UVB												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	14/34 (41.2%)	10/27 (37.0%)	**RR 1.11** (0.59 to 2.10)	**41 more per 1,000** (from 152 fewer to 407 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Participant reported treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9 months, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	27/169 (16.0%)	20/173 (11.6%)	**RR 1.38** (0.81 to 2.37)	**44 more per 1,000** (from 22 fewer to 158 more)	⨁⨁◯◯ LOW	CRITICAL
Repigmentation ≥75% at 9 months, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	9/169 (5.3%)	4/173 (2.3%)	**RR 2.30** (0.72 to 7.34)	**30 more per 1,000** (from 6 fewer to 147 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment-related adverse events at 9 months, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	48/169 (28.4%)	24/173 (13.9%)	**RR 2.05** (1.32 to 3.18)	**146 more per 1,000** (from 44 more to 302 more)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Erythema (Grade 3 and 4) at 9 months in adults, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	20/130 (15.4%)	2/133 (1.5%)	**RR 10.23** (2.44 to 42.89)	**139 more per 1,000** (from 22 more to 630 more)	⊕⊕⊕◯ Moderate	CRITICAL
Erythema (Grade 3 and 4) at 9 mos. in children, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	7/39 (17.9%)	1/40 (2.5%)	**RR 7.18** (0.93 to 55.68)	**155 more per 1,000** (from 2 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Skin thinning at 9 mos. in adults, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/130 (1.5%)	5/133 (3.8%)	**RR 0.41** (0.08 to 2.07)	**22 fewer per 1,000** (from 35 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL
Skin thinning at 9 mos. in children, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	0/39 (0.0%)	1/40 (2.5%)	**RR 0.34** (0.01 to 8.14)	**16 fewer per 1,000** (from 25 fewer to 179 more)	⨁◯◯◯ VERY LOW	CRITICAL
Change in CHU9D at 9 mos. in children, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	40	40	-	MD **0.01 lower** (0.04 lower to 0.02 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Change in VitiQoL at 21 mos. follow-up in adults, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	130	133	-	MD **0.8 higher** (6.86 lower to 8.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Change in Skindex 29 in adults at 21 months follow-up, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	130	133	-	MD **2 lower** (7.81 lower to 3.81 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Change in EQ-5D at 9 months., Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	169	173	-	MD **0.07 higher** (0.03 higher to 0.11 higher)	⨁⨁⨁⨁ MODERATE	CRITICAL
Participant reported loss of treatment response at 21 months follow-up in those with treatment success at 9 months, Hand-held NB-UVB vs. topical corticosteroid (mometasone furoate 0.1%)												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	10/27 (37.0%)	6/20 (30.0%)	**RR 1.23** (0.54 to 2.83)	**69 more per 1,000** (from 138 fewer to 549 more)	⨁⨁◯◯ LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, home-based hand-held phototherapy vs. institution-based excimer lamp												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	11/22 (50.0%)	8/22 (36.4%)	**RR 1.38** (0.69 to 2.75)	**138 fewer per 1,000** (from 113 fewer to 636 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, home-based hand-held phototherapy vs. institution-based excimer lamp												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	16/22 (72.7%)	12/22 (54.5%)	**RR 1.33** (0.84 to 2.11)	**180 more per 1,000** (from 87 fewer to 605 more)	⨁⨁◯◯ LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 16-week follow-up, home-based hand-held treatment NB-UVB vs. placebo												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	2/19 (10.5%)	0/10 (0.0%)	**RR 2.75** (0.14 to 52.33)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Erythema in patients at 16-week (per participant) follow-up, home-based hand-held treatment NB-UVB vs. placebo												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	13/19 (68.4%)	2/10 (20.0%)	**RR 3.42** (0.95 to 12.26)	**484 more per 1,000** (from 10 fewer to 1,000 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Pruritus in patients at 16-week follow-up, home-based hand-held NB-UVB treatment vs. placebo												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	2/19 (10.5%)	0/10 (0.0%)	**RR 2.75** (0.14 to 52.33)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Hyperpigmentation in patients at 16-week follow-up, home-based hand-held NB-UVB treatment vs. placebo												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	3/19 (15.8%)	0/10 (0.0%)	**RR 3.85** (0.22 to 67.93)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Dry skin in patients at 16-week follow-up, home-based hand-held NB-UVB treatment vs. placebo												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	3/19 (15.8%)	0/10 (0.0%)	**RR 3.85** (0.22 to 67.93)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Cold sores in patients at 16-week follow-up, home-based hand-held NB-UVB treatment vs. placebo												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	1/19 (5.3%)	0/10 (0.0%)	**RR 1.65** (0.07 to 37.18)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
QoL (DLQI) in patients at 16-week follow-up, home-based hand-held home NB-UVB phototherapy vs. placebo												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	19	10	-	MD **0.5 higher** (3.05 lower to 4.05 higher)	⨁⨁◯◯ LOW	CRITICAL
Cessation of spreading of vitiligo lesions at 16-week follow-up, home-based hand-held home NB-UVB phototherapy vs. placebo												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	22/56 (39.3%)	13/28 (46.4%)	**RR 0.85** (0.51 to 1.41)	**70 fewer per 1,000** (from 190 more to 228 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Adverse events in patients at 6-month follow-up, afamelanotide + NB-UVB vs. NB-UVB												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	23/28 (82.1%)	25/27 (92.6%)	**RR 0.89** (0.72 to 1.09)	**102 fewer per 1,000** (from 83 more to 259 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. tacrolimus 0.1% + Bioskin												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [b]	not applicable	not serious	not serious	none	72/100 (72.0%)	45/59 (76.3%)	**RR 0.94** (0.78 to 1.14)	**46 fewer per 1,000** (from 107 more to 168 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. tacrolimus 0.1% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	56/59 (94.9%)	**RR 0.97** (0.89 to 1.05)	**28 fewer per 1,000** (from 47 more to 104 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. pimecrolimus 1% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	72/100 (72.0%)	48/63 (76.2%)	**RR 0.94** (0.79 to 1.14)	**46 fewer per 1,000** (from 107 more to 160 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. pimecrolimus 1% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	61/63 (96.8%)	**RR 0.95** (0.88 to 1.02)	**48 fewer per 1,000** (from 19 more to 116 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. betamethasone dipropionate 0.05% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	25/28 (89.3%)	**RR 0.81** (0.68 to 0.96)	**170 fewer per 1,000** (from 36 fewer to 286 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. betamethasone dipropionate 0.05% + Bioskin												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	27/28 (96.4%)	**RR 0.95** (0.87 to 1.05)	**48 fewer per 1,000** (from 48 more to 125 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. calcipotriol ointment 0.005% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	45/60 (75.0%)	**RR 0.96** (0.79 to 1.16)	**30 fewer per 1,000** (from 120 more to 157 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. calcipotriol ointment 0.005% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	53/60 (88.3%)	**RR 1.04** (0.93 to 1.16)	**35 more per 1,000** (from 62 fewer to 141 more)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. L-phenylalanine 10% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	72/100 (72.0%)	45/60 (75.0%)	**RR 0.96** (0.79 to 1.16)	**30 fewer per 1,000** (from 120 more to 157 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. L-phenylalanine 10% + Bioskin												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	52/60 (86.7%)	**RR 1.06** (0.95 to 1.19)	**52 more per 1,000** (from 43 fewer to 165 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. tacrolimus 0.1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	13/22 (59.1%)	**RR 1.22** (0.84 to 1.76)	**130 more per 1,000** (from 95 fewer to 449 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. tacrolimus 0.1%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	92/100 (92.0%)	17/22 (77.3%)	**RR 1.19** (0.94 to 1.50)	**147 more per 1,000** (from 46 fewer to 386 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. pimecrolimus 1%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	10/19 (52.6%)	**RR 1.37** (0.88 to 2.13)	**195 more per 1,000** (from 63 fewer to 595 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. pimecrolimus 1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	92/100 (92.0%)	13/19 (68.4%)	**RR 1.34** (0.99 to 1.83)	**233 more per 1,000** (from 7 fewer to 568 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. betamethasone dipropionate 0.05%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	16/23 (69.6%)	**RR 1.03** (0.77 to 1.39)	**21 more per 1,000** (from 160 fewer to 271 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. betamethasone dipropionate 0.05%												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	22/23 (95.7%)	**RR 0.96** (0.87 to 1.07)	**38 fewer per 1,000** (from 67 more to 124 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. calcipotriol ointment 0.005%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	11/18 (61.1%)	**RR 1.18** (0.80 to 1.74)	**110 more per 1,000** (from 122 fewer to 452 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. calcipotriol ointment 0.005%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	92/100 (92.0%)	13/18 (72.2%)	**RR 1.27** (0.95 to 1.71)	**195 more per 1,000** (from 36 fewer to 513 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, Bioskin vs. L-phenylalanine 10%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	72/100 (72.0%)	5/18 (27.8%)	**RR 2.59** (1.22 to 5.51)	**442 more per 1,000** (from 61 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, Bioskin vs. L-phenylalanine 10%												
1	observational studies	serious [b]	not applicable	not serious	not serious	none	92/100 (92.0%)	6/18 (33.3%)	**RR 2.76** (1.43 to 5.32)	**587 more per 1,000** (from 143 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in lesions at 6-month follow-up, NB-UVB + catalase-superoxide (vitix gel) vs. NB-UVB												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/21 (4.8%)	0/21 (0.0%)	**RR 3.00** (0.13 to 69.70)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in lesions at 6-month follow-up, NB-UVB + catalase-superoxide (Vitix gel) vs. NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	5/21 (23.8%)	2/21 (9.5%)	**RR 2.50** (0.54 to 11.48)	**143 more per 1,000** (from 44 fewer to 998 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 36 wks. follow-up, PUVA vs. PUVA sol												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	5/18 (27.8%)	0/17 (0.0%)	**RR 10.42** (0.62 to 175.25)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 36 wks. follow-up, PUVA vs. PUVA sol												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	5/18 (27.8%)	1/17 (5.9%)	**RR 4.72** (0.61 to 36.39)	**219 more per 1,000** (from 23 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥ 75% (>75%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	3/8 (37.5%)	**RR 0.67** (0.15 to 2.98)	**124 fewer per 1,000** (from 319 fewer to 742 more)	⨁◯◯◯ VERY LOW	CRITICAL
Complete repigmentation (100%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	3/8 (37.5%)	**RR 0.33** (0.04 to 2.56)	**251 fewer per 1,000** (from 360 fewer to 585 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	4/8 (50.0%)	**RR 1.00** (0.38 to 2.66)	**0 fewer per 1,000** (from 310 fewer to 830 more)	⊕◯◯◯ VERY LOW	CRITICAL
Burning-pain in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	1/8 (12.5%)	**RR 2.00** (0.22 to 17.89)	**125 more per 1,000** (from 98 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	2/8 (25.0%)	**RR 1.00** (0.18 to 5.46)	**0 fewer per 1,000** (from 205 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥ 50% (>50%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	4/8 (50.0%)	**RR 1.00** (0.38 to 2.66)	**0 fewer per 1,000** (from 310 fewer to 830 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	3/8 (37.5%)	**RR 1.33** (0.43 to 4.13)	**124 more per 1,000** (from 214 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Complete repigmentation (100%) in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	3/8 (37.5%)	3/8 (37.5%)	**RR 1.00** (0.28 to 3.54)	**0 fewer per 1,000** (from 270 fewer to 953 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	3/8 (37.5%)	4/8 (50.0%)	**RR 0.75** (0.24 to 2.33)	**125 fewer per 1,000** (from 380 fewer to 665 more)	⨁◯◯◯ VERY LOW	CRITICAL
Burning-pain in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	1/8 (12.5%)	**RR 1.00** (0.07 to 13.37)	**0 fewer per 1,000** (from 116 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	2/8 (25.0%)	**RR 0.50** (0.06 to 4.47)	**125 fewer per 1,000** (from 235 fewer to 867 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	5/8 (62.5%)	4/8 (50.0%)	**RR 1.25** (0.52 to 3.00)	**125 more per 1,000** (from 240 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥ 75% (>75%) in patients at 3-month follow-up, MEL + khellin 4% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	3/8 (37.5%)	**RR 1.33** (0.43 to 4.13)	**124 more per 1,000** (from 214 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Complete repigmentation (100%) in patients at 3-month follow-up, MEL + khellin 4% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	3/8 (37.5%)	**RR 0.67** (0.15 to 2.98)	**124 fewer per 1,000** (from 319 fewer to 742 more)	⨁◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 3-month follow-up, MEL + khellin 4% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	5/8 (62.5%)	4/8 (50.0%)	**RR 1.25** (0.52 to 3.00)	**125 more per 1,000** (from 240 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Burning-pain in patients at 3-month follow-up, MEL + khellin 4% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	1/8 (12.5%)	**RR 2.00** (0.22 to 17.89)	**125 more per 1,000** (from 98 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patients at 3-month follow-up, MEL + khellin 4% vs. MEL												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	2/8 (25.0%)	**RR 0.50** (0.06 to 4.47)	**125 fewer per 1,000** (from 235 fewer to 867 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% (>50%) in patients at 3-month follow-up, MEL + khellin 4% vs. MEL												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	6/8 (75.0%)	4/8 (50.0%)	**RR 1.50** (0.67 to 3.34)	**250 more per 1,000** (from 165 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, CO2 laser + NB-UVB vs. CO2 laser												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	1/20 (5.0%)	2/20 (10.0%)	**RR 0.50 (0.05 to 5.08)**	**50 fewer per 1,000 (from 95 fewer to 408 more)**	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, CO2 laser + PRP vs. CO2 laser												
1	Randomized trials	Serious [b]	not applicable	not serious	Serious [a]	none	8/20 (40.0%)	2/20 (10.0%)	**RR 4.00** (0.97 to 16.55)	**300 more per 1,000** (from 3 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, CO2 laser vs. PRP												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	2/20 (10.0%)	4/20 (20.0%)	**RR 0.50** (0.10 to 2.43)	**100 fewer per 1,000** (from 180 fewer to 286 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, NB-UVB + microneedling + topical triamcinolone vs. NB-UVB												
1	Randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	6/20 (30.0%)	0/20 (0.0%)	**RR 13.00** (0.78 to 216.39)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 5-month follow-up, NB-UVB + microneedling + topical triamcinolone vs. NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	Serious [b]	not applicable	not serious	not serious [a]	none	14/20 (70.0%)	4/20 (20.0%)	**RR 3.50** (1.39 to 8.80)	**500 more per 1,000** (from 78 more to 1,000 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in QoL (DLQI) in patients at 6-month follow-up, OCG + UVB vs. UVB												
1	Randomized trials	serious [b]	not applicable	not serious	serious [a]	none	48	48	-	MD **0.53 lower** (2.35 lower to 1.28 higher)	⨁⨁◯◯ LOW	CRITICAL
Change in QoL (Embarassment) in patients at 6-month follow-up, yiqiqubai granule + 308nm excimer laser vs. 308 nm excimer laser												
1	Randomized trials	not serious	not applicable	not serious	not serious	none	80	78	-	MD **0.7 lower** (1.01 lower to 0.39 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Change in QoL (Dress) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. 308 nm excimer laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	not serious	not applicable	not serious	serious [a]	none	80	78	-	MD **0.2 lower** (0.56 lower to 0.16 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Change in QoL (Social) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. 308nm excimer laser												
1	Randomized trials	not serious	not applicable	not serious	not serious	none	80	78	-	MD **0.4 lower** (0.68 lower to 0.12 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Change in QoL (Work) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. 308 nm excimer laser												
1	Randomized trials	not serious	not applicable	not serious	not serious	none	80	78	-	MD **0.3 lower** (0.59 lower to 0.01 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥ 50% in patients at 6-month follow-up, yiqiqubai granule + 308nm excimer laser vs. 308nm excimer laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	Randomized trials	not serious	not applicable	not serious	serious [a]	none	45/80 (56.3%)	34/78 (43.6%)	**RR 1.29** (0.94 to 1.77)	**126 more per 1,000** (from 26 fewer to 336 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥ 75% in patients at 3-month post-treatment follow-up, PRP + excimer laser vs. excimer laser												
1	Randomized trials	not serious	not applicable	not serious	not serious	none	9/26 (34.6%)	0/26 (0.0%)	**RR 19.00** (1.16 to 310.37)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥ 50% in patients at 3-month post-treatment follow-up, PRP + excimer laser vs. excimer laser												
1	Randomized trials	not serious	not applicable	not serious	not serious	none	22/26 (84.6%)	9/26 (34.6%)	**RR 2.44** (1.41 to 4.25)	**498 more per 1,000** (from 142 more to 1,000 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Change in DLQI in patients at 24-week follow-up, Apremilast + NB-UVB vs. placebo + NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Light/laser therapies	Control	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	32	32	-	MD **0.72 higher** (1.16 lower to 2.6 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Complete repigmentation in lesions at 12-week follow-up, tacrolimus 0.1% + excimer laser vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	26/77 (33.8%)	15/78 (19.2%)	**RR 1.76** (1.01 to 3.05)	**146 more per 1,000** (from 2 more to 394 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, tacrolimus 0.1% + excimer laser vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	33/77 (42.9%)	30/78 (38.5%)	**RR 1.11** (0.76 to 1.63)	**42 more per 1,000** (from 92 fewer to 242 more)	⊕⊕◯◯ LOW	IMPORTANT
Complete repigmentation in lesions at 12-week follow-up, pimecrolimus 1% + excimer laser vs. excimer laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	17/74 (23.0%)	15/78 (19.2%)	**RR 1.19** (0.64 to 2.21)	**37 more per 1,000** (from 69 fewer to 233 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, pimecrolimus 1% + excimer laser vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	37/74 (50.0%)	30/78 (38.5%)	**RR 1.30** (0.91 to 1.87)	**115 more per 1,000** (from 35 fewer to 335 more)	⨁⨁◯◯ LOW	IMPORTANT
Complete repigmentation in lesions at 12-week follow-up, halometasone + excimer laser vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	33/82 (40.2%)	15/78 (19.2%)	**RR 2.09** (1.24 to 3.54)	**210 more per 1,000** (from 46 more to 488 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, halometasone + excimer laser vs. excimer laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	36/82 (43.9%)	30/78 (38.5%)	**RR 1.14** (0.79 to 1.66)	**54 more per 1,000** (from 81 fewer to 254 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Complete repigmentation in lesions at 12-week follow-up, excimer laser + tacrolimus 0.1% vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	14/57 (24.6%)	7/53 (13.2%)	**RR 1.86** (0.81 to 4.25)	**114 more per 1,000** (from 25 fewer to 429 more)	⨁⨁◯◯ LOW	CRITICAL
Repigmentation ≥ 50% (> 50%) in lesions at 12-week follow-up, excimer laser + tacrolimus 0.1% vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	43/57 (75.4%)	23/53 (43.4%)	**RR 1.74** (1.24 to 2.45)	**321 more per 1,000** (from 104 more to 629 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Complete repigmentation in lesions at 12-week follow-up, excimer laser + halometasone vs. excimer laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	25/71 (35.2%)	7/53 (13.2%)	**RR 2.67** (1.25 to 5.69)	**221 more per 1,000** (from 33 more to 619 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, excimer laser + halometasone vs. excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	32/71 (45.1%)	16/53 (30.2%)	**RR 1.49** (0.92 to 2.42)	**148 more per 1,000** (from 24 fewer to 429 more)	⨁⨁◯◯ LOW	IMPORTANT
Repigmentation ≥ 75% (>75%) in patients at 3-month follow-up, Home-b NB-UVB vs. Hospital-b NB-UVB												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	12/61 (19.7%)	9/61 (14.8%)	**RR 1.33** (0.61 to 2.93)	**49 more per 1,000** (from 58 fewer to 285 more)	⨁⨁◯◯ LOW	CRITICAL
Change in VitiQoL scores in patients at 20-week follow-up, Home-b NB-UVB vs. Hospital-b NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	not serious	none	61	61	-	MD **4.6 higher** (3.36 higher to 5.83 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥ 50% (>50%) in patients at 3-month follow-up, Home-b NB-UVB vs. Hospital-b NB-UVB												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	23/61 (37.7%)	24/61 (39.3%)	**RR 0.96** (0.61 to 1.50)	**16 fewer per 1,000** (from 153 fewer to 197 more)	⨁⨁◯◯ LOW	IMPORTANT
Repigmentation ≥ 75% (> 75%) in patients at 12-week follow-up, Vitilinex + NB-UVB vs. NB-UVB												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	16/24 (66.7%)	6/16 (37.5%)	**RR 1.78** (0.89 to 3.55)	**293 more per 1,000** (from 41 fewer to 956 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Repigmentation ≥ 50% (> 50%) in patients at 12-week follow-up, Vitilinex + NB-UVB vs. NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	20/24 (83.3%)	10/16 (62.5%)	**RR 1.33** (0.88 to 2.03)	**206 more per 1,000** (from 75 fewer to 644 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥ 75% in patients at 6-month follow-up, home-based NB-UVB vs. outpatient NB-UVB												
1	observational studies	not serious	not applicable	not serious	not serious	none	2/48 (4.2%)	3/46 (6.5%)	**RR 0.64** (0.11 to 3.65)	**23 fewer per 1,000** (from 58 fewer to 173 more)	⨁⨁◯◯ LOW	CRITICAL
Painful erythema in patients at 6-month follow-up, home-based NB-UVB vs. outpatient NB-UVB												
1	observational studies	not serious	not applicable	not serious	very serious [a]	none	5/48 (10.4%)	4/46 (8.7%)	**RR 1.20** (0.34 to 4.19)	**17 more per 1,000** (from 57 fewer to 277 more)	⨁◯◯◯ VERY LOW	CRITICAL
Pruritus in patients at 6-month follow-up, home-based NB-UVB vs. outpatient NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not applicable	not serious	very serious [a]	none	8/48 (16.7%)	8/46 (17.4%)	**RR 0.96** (0.39 to 2.34)	**7 fewer per 1,000** (from 106 fewer to 233 more)	⊕◯◯◯ VERY LOW	CRITICAL
Skin-burning in patients at 6-month follow-up, home-based NB-UVB vs. outpatient NB-UVB												
1	observational studies	not serious	not applicable	not serious	very serious [a]	none	2/48 (4.2%)	1/46 (2.2%)	**RR 1.92** (0.18 to 20.42)	**20 more per 1,000** (from 18 fewer to 422 more)	⊕◯◯◯ VERY LOW	CRITICAL
Change in QoL (vitiQoL) in patients at 6-month follow-up, home-based NB-UVB vs. outpatient-NB-UVB												
1	observational studies	not serious	not applicable	not serious	very serious [a]	none	48	46	-	MD **1.1 lower** (6.01 lower to 3.81 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% in patients at 6-month follow-up, home-based NB-UVB vs. outpatient NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Light/laser therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not applicable	not serious	very serious [a]	none	18/48 (37.5%)	18/46 (39.1%)	**RR 0.96** (0.57 to 1.60)	**16 fewer per 1,000** (from 168 fewer to 235 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Combination therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥75% (>75%) in patients at 3-month follow-up, alpha lipoic acid + betamethasone injection + NB-UVB vs. placebo + betamethasone injection + NB-UVB												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	5/26 (19.2%)	1/24 (4.2%)	**RR 4.62** (0.58 to 36.73)	**151 more per 1,000** (from 18 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 6-month follow-up, alpha lipoic acid + betamethasone injection + NB-UVB vs. placebo + betamethasone injection + NB-UVB												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	Serious [b]	not applicable	not serious	very serious [a]	none	11/26 (42.3%)	7/24 (29.2%)	**RR 1.45** (0.67 to 3.13)	**131 more per 1,000** (from 96 fewer to 621 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 3-month follow-up, alpha lipoic acid + betamethasone injection + NB-UVB vs. placebo + betamethasone injection + NB-UVB												
1	randomized trials	not serious	not applicable	not serious	serious [a]	none	11/26 (42.3%)	5/24 (20.8%)	**RR 2.03** (0.83 to 4.99)	**215 more per 1,000** (from 35 fewer to 831 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥50% (>50%) in patients at 6-month follow-up, alpha lipoic acid + betamethasone injection + NB-UVB vs. placebo + betamethasone injection + NB-UVB												
1	randomized trials	Serious [b]	not applicable	not serious	very serious [a]	none	18/26 (69.2%)	16/24 (66.7%)	**RR 1.04** (0.71 to 1.52)	**27 more per 1,000** (from 193 fewer to 347 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Cosmetic acceptability in patients at 6-month follow-up, punch grafting + corticosteroids vs. punch grafting + PUVA												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	24/28 (85.7%)	20/22 (90.9%)	**RR 0.94** (0.77 to 1.15)	**55 fewer per 1,000** (from 136 more to 209 fewer)	⊕⊕◯◯ LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	4/8 (50.0%)	**RR 0.50** (0.13 to 2.00)	**250 fewer per 1,000** (from 435 fewer to 500 more)	⊕◯◯◯ VERY LOW	CRITICAL
Complete repigmentation (100%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	3/8 (37.5%)	**RR 0.33** (0.04 to 2.56)	**251 fewer per 1,000** (from 360 fewer to 585 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Erythema in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	3/8 (37.5%)	**RR 1.33** (0.43 to 4.13)	**124 more per 1,000** (from 214 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Burning-pain in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	1/8 (12.5%)	**RR 2.00** (0.22 to 17.89)	**125 more per 1,000** (from 98 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	1/8 (12.5%)	**RR 2.00** (0.22 to 17.89)	**125 more per 1,000** (from 98 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 3-month follow-up, MEL+ khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	5/8 (62.5%)	**RR 0.80** (0.33 to 1.92)	**125 fewer per 1,000** (from 419 fewer to 575 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	2/8 (25.0%)	4/8 (50.0%)	**RR 0.50** (0.13 to 2.00)	**250 fewer per 1,000** (from 435 fewer to 500 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Control	Relative (95% CI)	Absolute (95% CI)		
Complete repigmentation (100%) in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	2/8 (25.0%)	**RR 0.50** (0.06 to 4.47)	**125 fewer per 1,000** (from 235 fewer to 867 more)	⊕◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	4/8 (50.0%)	5/8 (62.5%)	**RR 0.80** (0.33 to 1.92)	**125 fewer per 1,000** (from 419 fewer to 575 more)	⊕◯◯◯ VERY LOW	CRITICAL
Burning-pain in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	2/8 (25.0%)	2/8 (25.0%)	**RR 1.00** (0.18 to 5.46)	**0 fewer per 1,000** (from 205 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patients at 3-month follow-up, MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	2/8 (25.0%)	1/8 (12.5%)	**RR 2.00** (0.22 to 17.89)	**125 more per 1,000** (from 98 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 3-month follow-up, MEL+ khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	6/8 (75.0%)	**RR 0.67** (0.30 to 1.48)	**247 fewer per 1,000** (from 360 more to 525 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL + khellin 4%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	4/8 (50.0%)	4/8 (50.0%)	**RR 1.00** (0.38 to 2.66)	**0 fewer per 1,000** (from 310 fewer to 830 more)	⊕◯◯◯ VERY LOW	CRITICAL
Complete repigmentation (100%) in patients at 3-month follow-up MEL + tacrolimus 0.1% vs. MEL +khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	3/8 (37.5%)	2/8 (25.0%)	**RR 1.50** (0.34 to 6.70)	**125 more per 1,000** (from 165 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	3/8 (37.5%)	5/8 (62.5%)	**RR 0.60** (0.21 to 1.70)	**250 fewer per 1,000** (from 438 more to 494 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Control	Relative (95% CI)	Absolute (95% CI)		
Burning-pain in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	2/8 (25.0%)	**RR 0.50** (0.06 to 4.47)	**125 fewer per 1,000** (from 235 fewer to 867 more)	⨁◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patents at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL + khellin 4%												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	1/8 (12.5%)	1/8 (12.5%)	**RR 1.00** (0.07 to 13.37)	**0 fewer per 1,000** (from 116 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 3-month follow-up, MEL + tacrolimus 0.1% vs. MEL + khellin 4%												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	5/8 (62.5%)	6/8 (75.0%)	**RR 0.83** (0.43 to 1.63)	**128 fewer per 1,000** (from 428 fewer to 472 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. Mel + vitamin E												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	9/16 (56.3%)	4/16 (25.0%)	**RR 2.25** (0.87 to 5.83)	**313 more per 1,000** (from 33 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Erythema in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. MEL+ vitamin E												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	12/16 (75.0%)	6/16 (37.5%)	**RR 2** (1 to 4)	**375 more per 1,000** (from 0 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Control	Relative (95% CI)	Absolute (95% CI)		
Burning/pain in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. MEL+ vitamin E												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	6/16 (37.5%)	3/16 (18.8%)	**RR 2.00** (0.60 to 6.64)	**188 more per 1,000** (from 75 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Perilesional hyperpigmentation in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. MEL+ vitamin E												
1	observational studies	serious [b]	not applicable	not serious	very serious [a]	none	8/16 (50.0%)	5/16 (31.3%)	**RR 1.60** (0.67 to 3.84)	**188 more per 1,000** (from 103 fewer to 888 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. Mel + vitamin E												
1	observational studies	serious [b]	not applicable	not serious	serious [a]	none	14/16 (87.5%)	0.0%	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, CO2 laser + PRP vs. CO2 laser + NB-UVB												
1	randomized trials	serious [b]	not applicable	not serious	not serious	none	8/20 (40.0%)	1/20 (5.0%)	**RR 8.00** (1.10 to 58.19)	**350 more per 1,000** (from 5 more to 1,000 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Repigmentation ≥75% (>75%) in patients at 3-month follow-up, NB-UVB + microneedling + topical triamcinolone vs. microneedling + topical triamcinolone												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	6/20 (30.0%)	3/20 (15.0%)	**RR 2.00** (0.58 to 6.91)	**150 more per 1,000** (from 63 fewer to 887 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 3-month follow-up, NB-UVB + microneedling + topical triamcinolone vs. microneedling + topical triamcinolone												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	14/20 (70.0%)	9/20 (45.0%)	**RR 1.56** (0.89 to 2.73)	**252 more per 1,000** (from 49 fewer to 779 more)	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete repigmentation in lesions at 12-week follow-up in lesions, excimer laser + tacrolimus 0.1% vs. excimer laser + halometasone												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	14/57 (24.6%)	25/71 (35.2%)	**RR 0.70** (0.40 to 1.21)	**106 fewer per 1,000** (from 211 fewer to 74 more)	⊕⊕◯◯ LOW	CRITICAL
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, excimer laser + tacrolimus 0.1% vs. excimer laser + halometasone												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	29/57 (50.9%)	32/71 (45.1%)	**RR 1.13** (0.79 to 1.62)	**59 more per 1,000** (from 95 fewer to 279 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Complete repigmentation in lesions at 12-week follow-up, tacrolimus 0.1% + excimer laser vs. pimecrolimus 1% + excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	26/77 (33.8%)	17/74 (23.0%)	**RR 1.47** (0.87 to 2.48)	**108 more per 1,000** (from 30 fewer to 340 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, tacrolimus 0.1% + excimer laser vs. pimecrolimus 1% + excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	serious [a]	none	33/77 (42.9%)	37/74 (50.0%)	**RR 0.86** (0.61 to 1.21)	**70 fewer per 1,000** (from 195 fewer to 105 more)	⊕⊕◯◯ LOW	IMPORTANT
Complete repigmentation in lesions at 12-week follow-up, tacrolimus 0.1% + excimer laser vs. halometasone + excimer laser												
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	26/77 (33.8%)	33/82 (40.2%)	**RR 0.84** (0.56 to 1.26)	**64 fewer per 1,000** (from 177 fewer to 105 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% (>50%) in lesions at 12-week follow-up, tacrolimus 0.1% + excimer laser vs. halometasone + excimer laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [b]	not applicable	not serious	very serious [a]	none	33/77 (42.9%)	36/82 (43.9%)	**RR 0.98** (0.68 to 1.39)	**9 fewer per 1,000** (from 140 fewer to 171 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Surgical therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation (≥90%) in lesions at 6-month follow-up, UTSG vs. MPG												
1	observational studies	Serious[a]	not applicable	not serious	Serious[b]	none	27/64 (42.2%)	22/75 (29.3%)	**RR 1.44** (0.91 to 2.26)	**129 more per 1,000** (from 26 fewer to 370 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥ 50% in lesions at 6-month follow-up, UTSG vs. MPG												
1	observational studies	serious [a]	not applicable	not serious	Serious[b]	none	56/64 (87.5%)	65/75 (86.7%)	**RR 1.01** (0.89 to 1.15)	**9 more per 1,000** (from 95 fewer to 130 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation (≥90%) in lesions at 6-month follow-up, UTSG vs. NCES												
1	observational studies	serious[a]	not applicable	not serious	very serious[b]	none	27/64 (42.2%)	14/31 (45.2%)	**RR 0.93** (0.58 to 1.51)	**32 fewer per 1,000** (from 190 fewer to 230 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% in lesions at 6-month follow-up, UTSG vs. NCES												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	serious[a]	not applicable	not serious	not serious	none	56/64 (87.5%)	28/31 (90.3%)	**RR 0.97** (0.84 to 1.12)	**27 fewer per 1,000** (from 108 more to 145 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Repigmentation (≥90%) in lesions at 6-month follow-up, NCES vs. MPG												
1	observational studies	serious[a]	not applicable	not serious	Serious[b]	none	14/31 (45.2%)	22/75 (29.3%)	**RR 1.54** (0.91 to 2.60)	**158 more per 1,000** (from 26 fewer to 469 more)	⊕◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% in lesions at 6-month follow-up, NCES vs. MPG												
1	observational studies	serious[a]	not applicable	not serious	not serious	none	28/31 (90.3%)	65/75 (86.7%)	**RR 1.04** (0.90 to 1.21)	**35 more per 1,000** (from 87 fewer to 182 more)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Repigmentation ≥ 75% in patients at 3-month post-treatment follow-up, NCES Blister roof graft vs. NCES partial-thickness epidermal cuts (Thiersch graft)												
1	randomized trials	not serious	not applicable	not serious	Serious[b]	none	18/20 (90.0%)	20/20 (100.0%)	**RR 0.90** (0.76 to 1.07)	**100 fewer per 1,000** (from 240 fewer to 70 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hyperpigmentation in patients at 3-month post-treatment follow-up, NCES Blister roof graft vs. NCES partial-thickness epidermal cuts (Thiersch graft)												
1	randomized trials	not serious	not applicable	not serious	not serious	none	20/20 (100.0%)	2/20 (10.0%)	**RR 8.20** (2.56 to 26.30)	**720 more per 1,000** (from 156 more to 1,000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Repigmentation ≥ 50% in patients at 3-month post-treatment follow-up, NCES Blister roof graft vs. NCES partial-thickness epidermal cuts (Thiersch graft)												
1	randomized trials	not serious	not applicable	not serious	Serious[b]	none	18/20 (90.0%)	20/20 (100.0%)	**RR 0.90** (0.76 to 1.07)	**100 fewer per 1,000** (from 240 fewer to 70 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Repigmentation ≥75% in lesions at 16-week follow-up, cold trypsinization preparation NCES vs. warm trypsinization preparation NCES												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [a]	not applicable	not serious	very serious[b]	none	20/22 (90.9%)	16/20 (80.0%)	**RR 1.14** (0.88 to 1.47)	**112 more per 1,000** (from 96 fewer to 376 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥75% in patients at 3-month post-treatment follow-up, microneedling + tacrolimus 0.1% vs. microneedling												
1	randomized trials	serious[a]	not applicable	not serious	not serious	none	20/30 (66.7%)	10/30 (33.3%)	**RR 2.00** (1.14 to 3.52)	**333 more per 1,000** (from 47 more to 840 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Erythema in patients over a 6-month treatment period, microneedling + tacrolimus 0.1% vs. microneedling												
1	randomized trials	serious[a]	not applicable	not serious	very serious[b]	none	7/30 (23.3%)	5/30 (16.7%)	**RR 1.40** (0.50 to 3.92)	**67 more per 1,000** (from 83 fewer to 487 more)	⨁◯◯◯ VERY LOW	CRITICAL
Pain in patients at 3-month post-treatment follow-up, tacrolimus 0.1% + microneedling vs. microneedling												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [a]	not applicable	not serious	very serious[b]	none	8/30 (26.7%)	11/30 (36.7%)	**RR 0.73** (0.34 to 1.55)	**99 fewer per 1,000** (from 242 fewer to 202 more)	⨁◯◯◯ VERY LOW	CRITICAL
Itching in patients at 3-month post-treatment follow-up, tacrolimus 0.1% + microneedling vs. microneedling												
1	randomized trials	serious [a]	not applicable	not serious	not serious	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⨁⨁⨁◯ MODERATE	CRITICAL
Repigmentation ≥ 50% in patients at 3-month post-treatment follow-up, microneedling + tacrolimus 0.1% vs. microneedling												
1	randomized trials	serious [a]	not applicable	not serious	not serious	none	23/30 (76.7%)	11/30 (36.7%)	**RR 2.09** (1.26 to 3.48)	**400 more per 1,000** (from 95 more to 909 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation ≥ 75% in patients at 3-month follow-up, NCORSHFS vs. NCES												
1	randomized trials	serious [a]	not applicable	not serious	Serious[b]	none	3/10 (30.0%)	2/10 (20.0%)	**RR 1.50** (0.32 to 7.14)	**100 more per 1,000** (from 136 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hyperpigmentation in patients at 3-month follow-up, NCORSHFS vs. NCES												
1	randomized trials	serious [a]	not applicable	not serious	very serious [b]	none	0/10 (0.0%)	4/10 (40.0%)	**RR 0.11** (0.01 to 1.83)	**356 fewer per 1,000** (from 396 fewer to 332 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mild scarring in patients at 3-month follow-up, NCORSHFS vs. NCES												
1	randomized trials	serious [a]	not applicable	not serious	very serious [b]	none	0/10 (0.0%)	2/10 (20.0%)	**RR 0.20** (0.01 to 3.70)	**160 fewer per 1,000** (from 198 fewer to 540 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% in patients at 3-month follow-up, NCORSHFS vs. NCES												
1	randomized trials	serious [a]	not applicable	not serious	very serious [b]	none	8/10 (80.0%)	6/10 (60.0%)	**RR 1.33** (0.74 to 2.41)	**198 more per 1,000** (from 156 fewer to 846 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥ 75% (>75%) in patients at 16-week post-treatment follow-up, follicular unit extraction (FUE) vs. plucking hair follicles (PHF)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical therapies**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [a]	not applicable	not serious	very serious [b]	none	3/15 (20.0%)	0/15 (0.0%)	**RR 7.00** (0.39 to 124.83)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥ 50% (50%) in patients at 16-week post-treatment follow-up, follicular unit extraction (FUE) vs. plucking hair follicles (PHF)												
1	randomized trials	serious [a]	not applicable	not serious	very serious [b]	none	6/15 (40.0%)	3/15 (20.0%)	**RR 2.00** (0.61 to 6.55)	**200 more per 1,000** (from 78 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Repigmentation ≥75% (>75%) in patients at 24-week post-treatment follow-up, NCES/NDCS (non-cultured dermal cell suspension) vs. NCES												
1	randomized trials	not serious	not applicable	not serious	not serious	none	17/20 (85.0%)	9/20 (45.0%)	**RR 1.89** (1.12 to 3.17)	**400 more per 1,000** (from 54 more to 977 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥50% (>50%) in patients at 24-week post-treatment follow-up, NCES/NDCS vs. NCES												

Certainty assessment							№ of patients		Effect		Certainty		Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical therapies	Control	Relative (95% CI)	Absolute (95% CI)			
1	randomized trials	not serious	not applicable	not serious	serious [b]	none	20/20 (100.0%)	17/20 (85.0%)	**RR 1.17** (0.96 to 1.43)	**144 more per 1,000** (from 34 fewer to 365 more)	⨁⨁⨁◯ MODERATE		IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Skin camouflage therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Skin camouflage	Control	Relative (95% CI)	Absolute (95% CI)		
Change in QoL (DLQI) in patients at 8-week follow-up, Sabgh vs. Exuviance												
1	randomized trials	not serious	not applicable	not serious	very serious [a]	none	18	16	-	MD **0.79 lower** (6.5 lower to 4.92 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Complementary therapies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Skin camouflage**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Change in QoL (DLQI) in patients at 6-month follow-up, OCG + UVB vs. OCG												
1	randomized trials	serious [a]	not applicable	not serious	not serious	none	48	48	-	MD **1.97 lower** (3.74 lower to 0.19 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, CO_2 laser + PRP vs. PRP												
1	randomized trials	serious [a]	not applicable	not serious	very serious	none	8/20 (40.0%)	4/20 (20.0%)	**RR 2.00** (0.72 to 5.59)	**200 more per 1,000** (from 56 fewer to 918 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 5-month follow-up, PRP vs. CO_2 laser												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Skin camouflage**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	serious [a]	not applicable	not serious	very serious[b]	none	4/20 (20.0%)	2/20 (10.0%)	**RR 2.00** (0.41 to 9.71)	**100 more per 1,000** (from 59 fewer to 871 more)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥75% (>75%) in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. Vitamin E												
1	observational studies	serious [a]	not applicable	not serious	serious [b]	none	9/16 (56.3%)	0/16 (0.0%)	**RR 19.00** (1.20 to 301.16)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Repigmentation ≥50% (>50%) in patients at 12 wks. follow-up, Mel + khel + vitamin E vs. vitamin E												
1	observational studies	serious [a]	not applicable	not serious	not serious	none	14/16 (87.5%)	1/16 (6.3%)	**RR 14.00** (2.08 to 94.24)	**813 more per 1,000** (from 68 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Change in QoL (Embarassment) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. yiqiqubai granule												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Skin camouflage**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	not serious	none	80	75	-	MD **0.7 lower** (1.01 lower to 0.39 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Change in QoL (Dress) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. yiqiqubai granule												
1	randomized trials	not serious	not applicable	not serious	serious [b]	none	80	75	-	MD **0.1 lower** (0.44 lower to 0.24 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Change in QoL (Social) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. yiqiqubai granule												
1	randomized trials	not serious	not applicable	not serious	serious [b]	none	80	75	-	MD **0.4 lower** (0.66 lower to 0.14 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Change in QoL (Work) in patients at 6-month follow-up, yiqiqubai granule + 308 nm excimer laser vs. yiqiqubai granule												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Skin camouflage**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not applicable	not serious	not serious	none	80	75	-	MD **0.6 lower** (0.88 lower to 0.32 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Repigmentation ≥ 50% in patients at 6-month follow-up, yiqiqubai granule + 308nm excimer laser vs. yiqiqubai granule												
1	randomized trials	not serious	not applicable	not serious	serious [b]	none	45/80 (56.3%)	26/75 (34.7%)	**RR 1.62** (1.13 to 2.34)	**215 more per 1,000** (from 45 more to 465 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Repigmentation >75% (≥ 75%) at 12-week follow-up, Vitilinex (herbal bio-actives) + NB-UVB vs. Vitilinex												
1	randomized trials	serious [a]	not applicable	not serious	not serious	none	16/24 (66.7%)	9/35 (25.7%)	**RR 2.59** (1.38 to 4.87)	**409 more per 1,000** (from 98 more to 995 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Skin camouflage	Control	Relative (95% CI)	Absolute (95% CI)		
Repigmentation > 50% (≥ 50%) in patients at 12-week follow-up, vitilinex (herbal bio-actives) + NB-UVB vs. vitilinex												
1	randomized trials	serious [a]	not applicable	not serious	not serious	none	20/24 (83.3%)	15/35 (42.9%)	**RR 1.94** (1.27 to 2.97)	**403 more per 1,000** (from 116 more to 844 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Depigmentation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depigmentation	Control	Relative (95% CI)	Absolute (95% CI)		
Depigmentation > 90% at 6-month follow-up, facial depigmentation vs. extra-facial depigmentation												
1	observational studies	not serious	not applicable	not serious	not serious	none	11/20 (55.0%)	17/20 (85.0%)	**RR 0.65** (0.42 to 1.00)	**298 fewer per 1,000** (from 493 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
High patient satisfaction at 6-month follow-up, facial depigmentation vs. extra-facial depigmentation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Depigmentation**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not applicable	not serious	serious [a]	none	12/20 (60.0%)	16/20 (80.0%)	**RR 0.75** (0.49 to 1.14)	**200 fewer per 1,000** (from 408 fewer to 112 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix E: Summary of included comparative studies

Systematic reviews

Topical therapies (Q1), systemic therapies (Q3), light and laser therapies (Q4, Q5), combination therapies (Q7), surgical therapies (Q8), psychological (Q9), and complementary therapies (Q11).

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Whitton, M. E. (2015). Cochrane	Yes	Yes	Yes	Yes	Yes	RCTs

Database Syst Rev 2: CD003263.[2]						

Comments: A systematic review to assess the effects of all therapeutic interventions (topical preparations, oral preparations, various forms of light therapy, surgical techniques, psychological therapy, and complementary therapy) used in the management of vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 430 studies were identified; 378 were excluded (title and abstract screening; no mention of randomisation; 52 remaining studies → 13 studies excluded (randomisation deemed insufficient or absent). In total, 39 RCTs were included plus the 57 identified in the 2010 review → 96 included studies.

The authors found only one study assessing psychological interventions, but the outcomes could not be included in the statistical analyses. The authors found no studies evaluating micropigmentation, depigmentation, or cosmetic camouflage.

Repigmentation (>75%)

A total of 53/96 studies, most of which were of combination treatments with light, assessed >75% repigmentation; 8/53 studies reported a statistically significant result for >75% repigmentation.[79,168,169,192,200,212-214]

Combination therapies were better than monotherapy in the following: calcipotriol + psoralen ultraviolet A (PUVA) vs. PUVA;[79] hydrocortisone-17-butyrate + excimer laser vs. excimer laser alone;[192] OMP of prednisolone + narrow band ultraviolet B (NB-UVB) vs. OMP;[168] azathioprine + PUVA vs. PUVA alone;[169] 8-Methoxypsoralen (8-MOP) plus sunlight versus psoralen alone.[214]

Additionally, in two studies ginkgo biloba was better than placebo[200] clobetasol propionate was better than PUVAsol (PUVA + sunlight).[212]

A total of 18 studies assessed surgical interventions[35,195,196,213,215-228]

Seven studies assessed grafts alone or in combination with light therapies, patients treated with split skin grafting plus PUVAsol were found to be better (RR 1.89, 95% CI 1.25-2.85) than those receiving mini punch grafts three months after treatment.[213] Suction blister grafts were assessed in three studies; melanocyte transplantation was assessed in five studies. Dermabrasion was assessed in two studies and one of the studies suggested that dermabrasion

was favoured over calcineurin inhibitors. But statistical analyses could not be performed due to the lack of sufficient data to allow for an appropriate analysis owing to the intra-participant study design.

The authors were only able to conduct one meta-analysis of three studies for the repigmentation >75% outcome.[173,229,230] The meta-analysis showed a non-statistically significant result of 60% more participants achieving >75% repigmentation in favour of NB-UVB compared with PUVA (three studies: RR 1.60, 95% CI 0.74-3.45; $I^2 = 0\%$).

However, none of the included studies reported long term follow up and the maximum follow-up time was one-year post-treatment.

Side effects

In total, 65 of the 96 studies reported side effects with topical treatments being the majority and reporting some of the following: itching, redness, skin thinning, telangiectasia, and atrophy.

Studies assessing topical preparations specifically topical corticosteroids, reported the most side effects. Neither mometasone furoate nor hydrocortisone had associated side effects.

Side effects reported in the 18 studies assessing surgical interventions included cobblestoning, depigmentation of the grafts, infection, graft displacement, and superficial scarring. Studies investigating melanocyte transplantation reported bacterial infection at the recipient site, halo phenomenon infection at the recipient site, hyperpigmentation, and scarring. Studies investigating dermabrasion reported delayed healing, oedema (when extremities were treated), and hypertrophic scars.

QoL

Only nine of the 96 included studies reported the impact of the intervention on the QoL; of the nine studies only one study assessing surgical interventions (autologous non-cultured epidermal cell suspension + sunlight exposure vs. autologous non-cultured extracted hair follicle outer root sheath cell suspension + sunlight exposure) reported a statistically significant ($p < 0.001$) improvement in the mean value of the DLQI score for both groups, however the decline in the DLQI score between the two groups was not statistically significant.[222]

Conclusions

Most of the studies reporting successful repigmentation were combinations of various interventions with light, indicating that this is an effective treatment for vitiligo. The authors concluded that since there is no cure for vitiligo, it is necessary to provide the patients with ways of coping with it as part of standard care.

Abbreviations: CI, confidence interval; DLQI, dermatology life quality index; NB-UVB, narrow band ultraviolet B; OMP, oral minipulse; PUVAsol, psoralen and ultraviolet light + sunlight; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio

Topical therapies (Q1), systemic therapies (Q3), light and laser therapies (Q4, Q5)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed - specify)
Matin, R. (2011). Clin Evid (Online) 2011.[3]	Yes	Yes	Yes	Yes	Yes	Mixed (systematic reviews, RCTs and observational studies)

Comments: A systematic review to assess the effects of medical treatments and of ultraviolet (UV) light treatments, for vitiligo in adults and children.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 25 publications were included in this systematic review.

Topical corticosteroids

Adults: There were no clinically important results identified from RCTs about the strengths of topical corticosteroids compared with each other or comparing the efficacy of topical corticosteroids on different parts of the body in adults with vitiligo. But there was a consensus that potent and very potent topical corticosteroid in localised vitiligo are a useful first line treatment, especially in newly formed lesions. A consensus was also agreed amongst clinicians that topical corticosteroid therapy would be chosen as first line treatment for localised vitiligo, generalised vitiligo, and stable vitiligo. However, long term use of topical corticosteroids was not advocated due to the irreversible side effects including skin atrophy, striae, and telangiectasia. Long standing lesions have been shown to be relatively resistant to local corticosteroid treatment.

Children: Topical corticosteroids can be chosen as a first line treatment for localised vitiligo, generalised vitiligo, and stable vitiligo.

Topical immunomodulators

Adults: Observational studies in vitiligo reported similar efficacy to topical corticosteroids, it was suggested that they may be useful for treating facial skin or eye lids where the risk of skin atrophy from topical corticosteroids or phototoxicity from phototherapy is very high. However, the authors concluded that further RCT evidence for their use in vitiligo is needed to confirm this, therefore the effectiveness of topical immunomodulators is unknown.

Children: There was no direct information from RCTs about whether tacrolimus, pimecrolimus or imiquimod are better than no treatment in the management of children with vitiligo.

Topical vitamin D analogues

Adults: There were no RCTs identified of sufficient quality which compared calcipotriol with placebo or no treatment. Calcipotriol was shown to have a slight light-saving effect when used in combination with UVB, and response is achieved at a lower dose of UVB, but calcipotriol does not increase the overall effectiveness of UVB treatment. The author concluded that topical vitamin D analogues are unlikely to be beneficial in vitiligo.

Children: There was no direct information from RCTs about the effects of vitamin D analogues in children with vitiligo.

Oral Levamisole

Adults: There were no RCTs found determining the benefits of oral levamisole as a sole agent in repigmentation in adults; the author concluded that the effectiveness of oral levamisole in vitiligo was unknown.

Children: Not reported

Oral corticosteroids

Adults: There was no direct information from RCTs about oral corticosteroids in the treatment of adults or children with vitiligo. The consensus was that the side effects of oral corticosteroids far outweigh any benefits that may be achieved in people with vitiligo; the author concluded that it is likely to be ineffective and harmful.

Children: Likely to be ineffective or harmful

PUVA

Adults: The evidence suggested that oral psoralens ultraviolet A (PUVA) is effective for vitiligo; the author concluded that oral PUVA is likely to be beneficial in adults. But oral PUVA is more likely to be recommended over topical PUVA. Compared with narrow band ultraviolet B (NB-UVB), it is not clear whether topical PUVA is more effective at 4 months at improving repigmentation in adults and children.

Children: PUVA (oral or topical) is not recommended for children below the age of 12 due to the risk of cataract formation, and an increased risk of skin cancer.

NB-UVB

Adults: Only weak RCT evidence was identified to support the use of NB-UVB as a safe and effective treatment of generalised vitiligo but due to the minimal side effects, it is the first line treatment of choice for people with moderate or severe generalised disease. NB-UVB is considered safe and effective by clinicians in the treatment of generalised vitiligo.

Children: There was no direct information from RCTs identified about the effects of NB-UVB in children with vitiligo only. But the consensus is that NB-UVB is safe and effective in children.

Abbreviations: NB-UVA, narrow band ultraviolet A; PUVA, psoralens ultraviolet A; RCT, randomized controlled trial; RR, relative risk; UV, ultraviolet

Topical therapies (Q1), light and laser therapies (Q4, Q5)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed - specify)
Bae, J. M. (2016). J Am Acad Dermatol 74: 907-915.[4]	Yes	Yes	Yes	Yes	No	RCTs

Comments: A systematic review to assess the efficacy of excimer laser/light in combination with topical therapy (calcineurin inhibitors, vitamin D3 analogue, and corticosteroids) compared with excimer laser/light monotherapy for vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 258 publications were identified →250 were excluded. Eight RCTs, involving 276 patients were included.

Repigmentation (≥75%)
A total of 4/8 included studies compared topical calcineurin inhibitor combination therapy versus excimer laser/light monotherapy.[188-191] Fixed effect pooling of the results showed that combination therapy had a statistically significant better effect on the treatment success of vitiligo [four studies: RR 1.93, 95% CI (1.28-2.91); NNT 4.5, 95% CI 2.9-10].
Three of the included studies compared the efficacy of excimer laser/light and topical vitamin-D3 analogue combination therapy with excimer laser/light monotherapy.[193,231,232]

Combination therapy showed a statistically significant better effect in one RCT [one study; RR 4.5, 95% CI (1.04-19.47)].[193]

One study showed a significantly better effect of topical corticosteroid (hydrocortisone 17-butyrate) in combination with excimer laser/light compared with excimer laser/light alone [one study; RR 2.57, 95% CI (1.20-5.50)].[192]

Conclusions
The authors concluded that topical calcineurin inhibitors in conjunction with excimer laser/light are more effective compared with excimer laser/light monotherapy. The evidence was deemed to be insufficient to support the beneficial effects of topical vitamin-D3 analogue and corticosteroid in combination with excimer laser/light.

Abbreviations: CI, confidence interval; EL, excimer laser; RCT, randomized controlled trial; RR, relative risk.

Light and laser therapies (Q4, Q5)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed - specify)
Sun, Y. (2015). J Dermatolog	Yes	Yes	Yes	Yes	Yes	RCTs

Treat 26: 347-353.[5]						

Comments: A systematic review to evaluate the efficacy and safety of 308 nm excimer (laser/lamp) monotherapy on vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

N.B. The x axis of the forest plots in this systematic review have been labelled incorrectly, however the results are reported correctly.

Summary:

Study selection

A total of 695 potentially relevant publications were identified; 688 were excluded. Therefore, seven RCTs were eligible for inclusion and five of the seven RCTs were included in the meta-analysis.

Repigmentation

No significant differences were seen between 308 nm excimer laser and 308 nm excimer lamp on either ≥75% or ≥50% repigmentation rate, or between 308 nm excimer laser and narrow band ultraviolet B (NB-UVB) on either 100% or ≥ 75% repigmentation rate. More patients (two studies: RR 1.39, 95% CI 1.05-1.85; p=0.002)[233,234] or lesions (one study: RR 1.41, 95% CI 1.09-1.82; p=0.009)[233] achieved ≥50% repigmentation rate by 308nm excimer laser than by NB-UVB treatment.

Side effects

Six of the studies listed the side effects. The types, severity and number of side effects of 308 nm excimer laser were like those of 308 nm excimer lamp or NB-UVB with the most common ones being: erythema, itching, burning and blister, which were well tolerated. Overall, the side effects were minimal and tolerable.

Conclusions

The authors concluded that 308 nm excimer laser showed equivalent efficacies to 308 nm excimer lamp control and NB-UVB control concerning ≥ 75% repigmentation rate of vitiligo patches.

Abbreviations: NB-UVB, narrow band ultraviolet B; RCT, randomized controlled trial; RR, relative risk

Light and laser therapies (Q4, Q5)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed - specify)
Xiao, B.-H. (2015). J Dermatolog Treat 26: 340-346[6]	Yes	Yes	Yes	Yes	Yes	RCTs

Comments: A systematic review to assess the effect and safety of narrow band ultraviolet B (NB-UVB) compared with ultraviolet A (UVA), psoralens ultraviolet A (PUVA) or 308 nm excimer laser/light for vitiligo using an evidence-based approach.

Outcome measures listed match some of those set out in the guideline protocol.

N.B. The x axis of the forest plots in this systematic review have been labelled incorrectly, however the results reported are not statistically significant.

Summary:

Study selection

A total of 224 potentially relevant publications were identified; 217 publications were excluded. Therefore, seven RCTs were considered eligible for inclusion.

Repigmentation

Two trials compared NB-UVB with UVA control, showing no significant difference between the two methods on the number of patients who achieved > 60% repigmentation (two studies: RR, 2.50; 95% CI 0.11-56.97; p > 0.05).[235,236]

Two trials compared NB-UVB with PUVA, no statistically significant difference was shown between the two treatments on the number of patients who achieved >50% repigmentation (two studies: RR, 1.16; 95% CI 0.64-2.11; p> 0.05) or >75% repigmentation (two studies: RR, 2.00; 95% CI 0.89-4.48; p> 0.05).[168,229]

Three trials[220,237,238] compared NB-UVB with 308 nm excimer light/laser (the light sources were light in two trials and laser in one trial). The meta-analysis results of the two trials investigated excimer light showed no significant difference found between the two methods on the number of patients who achieved >50% repigmentation (two studies: RR, 1.10; 95% CI 0.16-7.72, p> 0.05) and >75% repigmentation (two studies: RR=0.55, 95% CI 0.03-9.01; p> 0.05).[237,238]

Side effects

The side effects were in general, well tolerated and minimal; the most frequently reported side effects were erythema, mild burning or pain, mild-to-moderate itching, and sensation of the skin.

Conclusions

The authors concluded that NB-UVB showed equivalent efficacies to UVA, PUVA and 308nm excimer laser/light in the treatment of vitiligo. Due to the small number and clinical heterogeneity of the eligible studies, more RCTs of high quality with homogenous information are needed to determine the clinical benefits of NB-UVB in the treatment of vitiligo.

Abbreviations: CI, confidence interval; NB-UVB, narrow band ultraviolet B; RCT, randomized controlled trial; RR, relative risk.

Light and laser therapies (Q4, Q5)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Chiu, Y.-J. (2018). Lasers in Medical Science 33: 1549-1556.[9]	Yes	Yes	No – search strategy not given, only search terms	Yes	Yes	Mixed (RCTs, non-randomized controlled trials, all within-patient)

Comments

A systematic review and meta-analysis to assess the safety and efficacy of fractional CO_2 laser as a combination therapy compared to conventional treatments in people with stable non-segmental vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

In total, 698 publications were identified from the literature search → 503 titles and abstracts were screened → 13 full-text publications were screened → 6 publications met the eligibility criteria and were included in the systematic review and meta-analysis.

Repigmentation (≥75%)

Combination therapy with fractional CO_2 laser compared with conventional therapies (topical corticosteroids, sun exposure, salicylic solution, and NB-UVB) was shown to be superior at achieving ≥75% repigmentation [6 studies, RR=2.80, 95% CI (1.29 - 6.07), p=0.009] [90,224,239-242]

Repigmentation (≥50%)

Combination therapy with fractional CO_2 laser compared with conventional therapies (topical corticosteroids, sun exposure, salicylic solutions and NB-UVB) was shown to be superior at achieving ≥50% repigmentation [6 studies, RR=2.62, 95% CI (1.58 - 4.34), p=0.0002] [90,224,239-242]

Adjusted analysis

The authors also performed an adjusted analysis removing one of the studies [242] as the treatment group received NB-UVB phototherapy, fractional CO_2 laser, followed by topical betamethasone compared with the control group participants who received NB-UVB therapy only.

- Combination therapy was shown to be marginally superior to conventional therapies at achieving ≥75% repigmentation, but this was not statistically significant [5 studies, RR=1.43, 95% CI (0.61 - 3.32), p=0.41]
- Combination therapy was shown to be superior to conventional therapies at achieving ≥50% repigmentation [5 studies, RR=2.56, 95% CI (1.32 - 4.95), p=0.005]

Side effects

The most common adverse effect was pain, followed by burning sensation, erythema, oedema, and oozing. No infection, scarring or Koebner phenomenon occurred following CO_2 laser treatment.

Study quality

- All studies lacked blinding, but this is due to the nature of laser treatment procedures
- Random sequence generation was unclear in five of the six included studies
- Allocation concealment information was unclear in all the included studies
- Funnel plots did not show the presence of publication bias

Limitations

- Small number of trials included
- Small sample size of the included studies
- Two of the included studies did not qualify as RCTs
- Different laser equipment used with varying protocols, number of treatments and follow-up parameters
- Shorter follow-up period of 12-wks.
- Data for childhood vitiligo wasn't evaluated
- All included studies were within-patient so this double-counts the number of participants

Conclusions

Fractional CO_2 laser in combination with conventional treatment is efficient and safe, it may also be considered as an adjunct therapeutic option for adult patients with refractive non-segmental vitiligo.

Abbreviations: CI, Confidence interval; CO_2 laser; NB-UVB, narrow band ultraviolet B; RCT, randomised controlled trial; RR, risk ratio; wk., week

Complementary therapies (Q11)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed - specify)
Chen, Y.-J. (2016). Complement	Yes	Yes	Yes	Yes	Yes	RCTs

Ther Med 26: 21-27[7]						

Comments: A systematic review to assess the effects of oral Chinese herbal medicine (CHM) combined with phototherapy for vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 686 potentially relevant publications were identified. Thirty duplicates were removed, and 651 publications were excluded. Therefore, five RCTs met the inclusion criteria and were included in the meta-analysis.

Repigmentation (>50%)

All the included RCTs assessed the outcome of > 50% repigmentation rate at 3-month follow-up, and most showed a significantly higher proportion of the combined oral CHM and phototherapy group compared with the control group. The meta-analysis revealed a statistically significant superior effectiveness in those receiving oral CHM in combination with narrow band ultraviolet B (NB-UVB) when compared with phototherapy alone (five studies: risk difference, 0.22; 95% CI 0.14-0.29; p<0.00001).[243-247]

N.B. There is added clinical heterogeneity due to each of the five RCTs assessing a different CHM formula.

Side effects

Only one of the five included RCTs did not report on side effects. The side effects reported by the remaining four RCTs were mild and without significant renal or liver function impairment.

QoL

Whilst the QoL was a primary outcome, none of the included trials reported on the quality of life.

Conclusions

The authors concluded that oral CHM in combination with NB-UVB had superior effectiveness in terms of repigmentation rate of vitiligo when compared with NB-UVB alone. However, the evidence is limited due to the short follow-up period and the low quality of trials included in this review.

Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; NB-UVB, narrow band ultraviolet B; QoL, quality of life; RCT, randomized controlled trial

Complementary therapies (Q11)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Szczurko, O. (2008). BMC Dermatol 8:2.[8]	Yes	Yes	Yes	Yes	Yes	Mixed (RCTs, non-randomized comparative studies)

Comments: A systematic review to assess the efficacy of natural health products (NHPs).

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 986 potentially relevant publications were identified; 971 were excluded. Therefore, 15 publications met the eligibility criteria and were deemed suitable for inclusion.

Repigmentation (threshold varied)

The most studied intervention was L-phenylalanine (three trials),[248-250] overall there was moderate evidence that it has efficacy as an adjuvant agent to ultraviolet A (UVA) or ultraviolet B (UVB) phototherapy.

Three clinical trials utilised a range of traditional Chinese medicine products, all three trials compared NHP intervention to conventional biomedical treatments of vitiligo (phototherapy, corticosteroids, or psoralen) in the control group.[251-253]

Six studies[200,254-258]investigated the use of plants in the treatment of vitiligo, four of these used plants as photosensitizing agents.[254-257] Overall there was weak evidence that photosensitizing plants can be effective in conjunction with phototherapy, and moderate evidence that Ginkgo biloba by itself can be useful for vitiligo.

Two trials[259,260] investigated the use of vitamins as adjuvants to UVA and UVB phototherapy, there was weak evidence for vitamin E as an adjunct to phototherapy.[260]

The quality of the trials identified was poor, most studies were poorly reported often lacking information about dosing frequency, dosage strength, participant withdrawal, statistical analyses, and randomisation. The authors expressed a similar concern to Whitton et al. (2015) concerning the variation in methods for scoring repigmentation, the repigmentation ranges seemed arbitrary and varied between trials, making data pooling and comparisons difficult.[2]

Conclusions
The authors concluded that whilst there are reports investigating the efficacy of NHPs for vitiligo, they are of poor methodological quality and contain significant reporting flaws. Most trials used NHPs as an adjuvant to UVA or UVB. L-phenylalanine used with phototherapy, and oral Ginkgo biloba as monotherapy showed promising results and warrants further investigation.

Abbreviations: NHPs, natural health products; RCT, randomized controlled trial; UVA, ultraviolet A; UVB, ultraviolet B

Light therapies (Q4)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Bae, J. M. (2017). JAMA Dermatol 153: 666-674.[13]	Yes	Yes	Yes	Yes	Yes	Mixed (RCTs and non-randomized comparative studies)
Comments: A systematic review and meta-analysis of all relevant prospective studies to determine the repigmentation rates of NB-UVB and PUVA phototherapy across different treatment durations in people with a diagnosis of generalised or symmetrical vitiligo. Outcome measures listed match some of those set out in the guideline protocol.						

Summary:

Study selection

A total of 572 potentially relevant publications were identified; 141 publications remained after the independent reviewers screened the titles and abstracts. Finally, 35 unique studies involving 1428 unique patients met the inclusion criteria. Of these, 29 studies with 1201 patients investigated NB-UVB and 9 studies with 227 patients investigated PUVA.

Repigmentation (≥75%)

Single-arm proportional meta-analysis was conducted.

NB-UVB:

A marked (≥75%repigmentation) response to NB-UVB phototherapy was achieved in 13.0%; (95% CI, 2.1%-23.9%) of 106 patients in 2 studies at 3 months, 19.2% (95% CI, 11.4%-27.0%) of 266 patients in 13 studies at 6 months, and 35.7% (95% CI, 21.5%-49.9%) of 540 patients in 9 studies at 12 months.

Depending on body site:

Marked responses were achieved on the face and neck in 44.2% (95% CI, 24.2%-64.2%) of 153 patients in 5 studies, on the trunk in 26.1% (95% CI, 8.7%-43.5%) of 134 patients in 5 studies, on the extremities in 17.3% (95% CI, 8.2%26.5%) of 162 patients in 5 studies, and on the hands and feet in none of 172 patients in 6 studies.

PUVA:

A marked response to PUVA phototherapy was achieved in 8.5% (95% CI, 0%-18.3%) of 88 patients in 3 studies at 6 months and 13.6% (95% CI, 4.2%-22.9%) of 72 patients in 3 studies at 12 months.

Conclusions

A longer treatment duration should be encouraged to enhance the treatment response, and at least 6 months is required to assess the responsiveness to phototherapy. The overall treatment response to NB-UVB therapy was better than to PUVA therapy. Most effective response was anticipated on the face and neck, whereas the hands and feet showed minimal response.

Abbreviations: CI, confidence interval; NB-UVB, narrow band ultraviolet B; PUVA, psoralens and ultraviolet A; RCT, randomized controlled trial

Light therapies (Q4)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Jin, J. (2016). IntJ Clin Exp Med 9: 18790-18798.[14]	Yes	Yes	Yes	No	Yes	RCTs

Comments: A systematic review and meta-analysis to evaluate the efficacy and safety of the combination therapy for vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 257 relevant publications were identified; 234 publications were excluded after screening of titles and abstracts. Overall, 23 full-text publications were reviewed by two independent investigators → 17 were excluded. A total of 6 studies, consisting of 235 patients were included in the meta-analysis.[188-190,192,193,231]

Repigmentation

The excimer laser/light alone group was significantly lower than the combination group in 75-100% repigmentation rate (five studies: RR=0.45, 95% CI: 0.32 – 0.65, $p<0.05$).[188-190,192,193]

There was no statistically significant difference observed for 50-75% repigmentation rate in the laser/light alone group compared with the combination group (four studies: RR=0.98, 95% CI: 0.64 – 1.51).[188-190,193]

In general, there were no statistically significant differences between the two treatment groups in the incident of side effects (four studies: RR=0.70, 95% CI: 0.37 – 1.31).[188,189,192,193]

Conclusions:
Combination therapy of excimer laser/light with a drug (included tacalcitol, calcipotriol, hydrocortisone, pimecrolimus, and tacrolimus) provided better clinical outcomes than monotherapy for the treatment of vitiligo. Subgroup analysis showed no differences between excimer laser and light in efficacy and safety profile.

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio

Topical therapies (Q1)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Kim, H. J. (2018). Acta dermato-venereologica 98: 180-184.[12]	Yes	Yes	Yes	Yes	Yes	Mixed

Comments: The aim of this systematic review was to investigate the effectiveness and safety of fractional CO_2 laser as an add-on treatment in patients with vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:
Study selection
A total of 222 publications were identified → 135 after duplicate removal → 10 full-text publications assessed after title and abstract screening → 6 studies included in the systematic review → 4 studies included in meta-analysis.[90,224,239,241]

The treatment regimens for both the treatment arm (fractional CO_2 laser + conventional treatment) and control arm (conventional treatment alone) differed among studies. The number of fractional CO_2 laser treatments varied from 1 to 10 sessions, with the treatment interval ranging from 1 week to 2 months.

Conventional treatment included topical agents (topical steroid, topical salicylic acid), UVB (NB-UVB, targeted UVB), sun exposure, and autologous hair transplant in several combinations.

Repigmentation
The addition of CO_2 laser to routine treatment modalities was superior to conventional treatment alone in achieving >50% repigmentation (3 studies: RR = 4.9, 95%CI: 1.15 – 20.93, p=0.03).

Adverse events:
Adverse effects were present in all studies, fractional CO_2 laser add-on to conventional vitiligo treatment caused transient pain, erythema, oedema, post-laser crust, tiny brown spots on the nail plate and slight oozing of the treated area. Most symptoms were relieved within a day and post-laser crusting disappeared within a week.

Conclusions:
Evidence from the systematic review and meta-analysis provides evidence to support that fractional CO_2 laser is valuable treatment for patients with vitiligo.

Abbreviations: CO_2, carbon dioxide; NB-UVB, narrow band ultraviolet B; RCT, randomized controlled trial; RR, risk ratio; Y, yes

Light therapies (Q4)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Li, R. (2017). Photodermatol Photoimmunol	Yes	Yes	Yes	Yes	Yes	RCTs

Photomed 33: 22-31.[10]						

Comments: The aim of this systematic review was to explore whether a combination of NB-UVB and topical agents would be superior to NB-UVB alone for treating vitiligo.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 909 publications were identified → 498 after duplicate removal → 22 full-text publications assessed for inclusion after title and abstract screening → 7 studies included in the systematic review and meta-analysis.[109,175,261-265]

Repigmentation ≥50% at 3-6 months

There was no statistically significant difference between combination therapy (NB-UVB and topical calcineurin inhibitor or NB-UVB and topical vitamin-D3) compared with NB-UVB monotherapy in achieving repigmentation ≥50%.

NB-UVB in combination with topical calcineurin inhibitors vs. NB-UVB alone, [three studies: RR=1.22, 95% (0.88 – 1.68), p=0.23][175,261,262]

NB-UVB in combination with topical vitamin-D3 analogs vs. NB-UVB alone, [three studies: RR=1.50, 95% CI (0.75 – 2.99), p=0.25][109,263,264]

Repigmentation ≥50% at 3-6 months on the face and neck

There was a statistically significant difference between combination therapy (NB-UVB and topical calcineurin inhibitor) compared with NB-UVB monotherapy in achieving repigmentation ≥50%.

NB-UVB in combination with topical calcineurin inhibitors vs. NB-UVB alone, [3 studies: RR=1.40, 95% CI (1.08 – 1.81), p=0.01][175,262,265]

Repigmentation ≥75% at 3-6 months

There was no statistically significant difference between combination therapy (NB-UVB and topical calcineurin inhibitor or NB-UVB and topical vitamin-D3) compared with monotherapy in achieving repigmentation ≥75%.

NB-UVB in combination with topical calcineurin inhibitors vs. NB-UVB alone, [2 studies: RR=1.84, 95% (0.90-3.78), p=0.09][175,262]

NB-UVB in combination with topical vitamin-D3 analogs vs. NB-UVB alone, [1 study: RR=0.67, 95% CI (0.21, 2.08), p=0.48][109]

Repigmentation ≥75% at 3-6 months on the face and neck

There was a statistically significant difference between combination therapy (NB-UVB and topical calcineurin inhibitor) compared with NB-UVB monotherapy in achieving repigmentation ≥75%.

NB-UVB in combination with topical calcineurin inhibitors vs. NB-UVB alone, [3 studies: RR=1.88, 95% CI (1.10 – 3.20), p=0.02][175,262,265]

Conclusions:

Adding neither topical calcineurin inhibitors nor vitamin-D3 analogs on NB-UVB can yield significantly superior outcomes than NB-UVB monotherapy for the treatment of vitiligo. But the meta-analysis showed that the addition of topical calcineurin inhibitors to NB-UVB may increase treatment outcomes in vitiligo affecting the face and neck, although a good option, the authors caution its use due to the increased risk of skin cancers.

Abbreviations: CI, confidence interval; N, no; NB-UVB, narrow band ultraviolet B; RCT, randomized controlled trial; RR, risk ratio; Y, yes

Combination therapies (Q7)

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Lommerts, J. E. (2018). J Eur Acad Dermatol Venereol 32: 1427 - 1435.[11]	Yes	Yes	Yes	Yes	Yes	Mixed (RCTs, non-randomized comparative studies, and case series)

Comments: A systematic review to identify evidence for the combination therapy of phototherapy and melanocyte transplantation.

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

A total of 1815 publications were identified → 1815 titles and abstracts were screened after duplicate removal → 418 full-text publications were assessed for eligibility → 39 studies consisting of 1624 patients were included in the systematic review.

Repigmentation:

Due to the high heterogeneity and unavailable data, the authors were not able to pool the data and compare the results between phototherapy modalities and perform a sub-analysis per vitiligo subtype.

The authors found limited evidence that phototherapy improves the outcome of melanocyte transplantation in vitiligo. There is insufficient evidence to recommend a specific type or regimen of phototherapy.

Conclusions:

There is some evidence that phototherapy improves the outcome of melanocyte transplantation in vitiligo. The authors recommend NB-UVB as a standard phototherapy after melanocyte transplantation. But the authors highlight that more prospective randomized controlled studies are needed to investigate the additional benefit of the different phototherapy modalities.

Abbreviations: N, no; NB-UVB, narrow band ultraviolet B; RCT, randomized controlled trial; Y, yes

Topicals

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Arora, C. J., M. Rafiq, et al. (2020). Australas J Dermatol 61(1): e1-e9.[15]	Yes	Yes	Yes	Yes	Yes	RCTs

Comments
A systematic review of RCTs to assess the efficacy and safety of tacrolimus as mono- and adjunctive therapy for vitiligo.

Outcome measures listed matches some of those set out in the guideline protocol.

Summary:

Study selection
A total of 987 publications were identified → 76 full-text were accessed for eligibility → 58 full-texts were excluded → manual searching identified one further publication → 19 RCTs met the eligibility criteria.

Repigmentation (>75%)
Tacrolimus + NB-UVB combination therapy was shown to be better than NB-UVB monotherapy at achieving >75% repigmentation.

Tacrolimus + NB-UVB vs. NB-UVB [2 studies, RR 1.34; 95% CI (1.05 – 1.71), p=0.02]

Tacrolimus and steroids had similar rates of achieving >75% repigmentation [RR 1.02; 95% CI (0.19 – 5.51), p=0.98] [Kathuria 2012; Rafiq 2016; Silpa-Archa 2016; Wazir 2010; Lepe 2003] But a high heterogeneity was found between the analysed studies [I^2 = 73%, p = 0.006]

Tacrolimus + CO_2 fractional laser combination was shown to be better than tacrolimus monotherapy at achieving > 75% repigmentation [2 studies, RR 2.11; 95% CI (0.87 – 5.09), p=0.10]

Excimer laser and tacrolimus combination compared with excimer laser monotherapy was shown to be better than excimer laser monotherapy at achieving > 75% repigmentation [2 studies, RR 2.39; 95% CI (0.64 – 8.96), p=0.20]. But a high heterogeneity was found between the analysed studies [I^2 = 73%, p=0.05]

Repigmentation >50%

There was no difference between corticosteroids and tacrolimus:
[5 studies, RR 0.85; 95% CI (0.68 – 1.06), p=0.15]

Excimer laser and tacrolimus combination therapy compared to excimer laser monotherapy were shown to be similar at achieving >50% repigmentation [2 studies, RR 2.11; 95% CI (0.87 – 5.09), p=0.10]

Quality of studies

- Random sequence generation showed an unclear risk of bias in over half of the studies
- Blinding of participants and personnel as well as blinding of outcome assessment showed a high risk of bias in 12 of 19 studies
- All studies, except for three, showed a low risk of bias relating to selective reporting

Conclusions

The authors concluded that combining tacrolimus with steroids or phototherapy or laser could be a superior option to using tacrolimus alone in achieving a higher repigmentation rate. But, due to the clinical heterogeneity of the included studies and the high risk of bias in some of the studies, the authors did not draw any solid conclusions on the superiority of combination vs. monotherapy tacrolimus treatment.

Abbreviations: CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio

Topical

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Lee, J. H., H. S. Kwon, et al. (2019). JAMA Dermatol. e1 – e11[16]	Yes	Yes	Yes	Partially Yes (only publication bias assessed)	Yes	Mixed (RCTs, cohort, within-patient, case series)

Comments

A systematic review to assess the treatment response to assess the treatment response in people with vitiligo to topical calcineurin inhibitor monotherapy and in combination with phototherapy.

Outcome measures listed match some of those set out in the guideline protocol.

Summary

<u>Study selection</u>

A total of 468 publications were identified through database searching → 250 titles and abstracts screened and an additional 5 publications were identified through related publications → 102 full-text publications were assessed for eligibility → 56 publications met the eligibility criteria.

Treatment response to topical calcineurin inhibitors in combination with phototherapy.

<u>Repigmentation (≥75%)</u>

In total, ≥75% repigmentation was achieved in 18.1%, 95% CI (13.2% - 23.1%), p<0.01 of 520 patients (in 19 studies) receiving topical calcineurin inhibitor monotherapy.

In total, ≥75% repigmentation was achieved in 47.5%, 95% CI (30.6% - 64.4%), p<0.01 of 490 patients (in nine studies) receiving topical calcineurin inhibitor and phototherapy combination.

In children, ≥75% repigmentation was achieved in 31.7%, 95% CI (6.7% - 56.8%) of patients (in five studies) receiving topical calcineurin inhibitor monotherapy.

On the face and neck, ≥75% repigmentation was achieved in 35.4 %, 95% CI (24.9% - 46.0%) of 353 patients (in 16 studies) receiving topical calcineurin inhibitor monotherapy.

On the face and neck, ≥75% repigmentation was achieved in 55.2%, 95% CI (24.6% - 85.9%) of 103 patients (in four studies) receiving topical calcineurin inhibitor and phototherapy combination.

On the trunk and extremities, ≥75% repigmentation was achieved in 2.3%, 95% CI (0.3% - 4.3%) of 185 patients (in eight studies) receiving topical calcineurin inhibitor monotherapy.

On the trunk and extremities, ≥75% repigmentation was achieved in 16.1%, 95% CI (10.2% - 22.0%) of 161 (in three studies) patients receiving topical calcineurin inhibitor and phototherapy combination.

<u>Repigmentation (≥50%)</u>

In total, ≥50% repigmentation was achieved in 38.5%, 95% CI (28.2% – 48.8%), p<0.01 of patients receiving topical calcineurin inhibitor monotherapy

In total, ≥50% repigmentation was achieved in 72.9%, 95% CI (57.6% – 88.2%), p<0.01 of patients receiving topical calcineurin inhibitor and phototherapy combination.

In children, ≥50% repigmentation was achieved in 47.3%, 95% CI (19.0% – 75.7%) of patients receiving topical calcineurin inhibitor monotherapy.
On the face and neck, ≥50% repigmentation was achieved in 57.5%, 95% CI (44.0% –70.7%) of patients receiving topical calcineurin inhibitor monotherapy.

On the face and neck, ≥50% repigmentation was achieved in 81.5%, 95% CI (10.3% – 92.7%) of patients receiving topical calcineurin inhibitor and phototherapy combination

On the trunk and extremities ≥50% repigmentation was achieved in 10.6%, 95% CI (5.3% – 15.8%) of patients receiving topical calcineurin inhibitor monotherapy.

On the trunk and extremities ≥50% repigmentation was achieved in 44.9%, 95% CI (30.3% –59.5%) of patients receiving topical calcineurin inhibitor and phototherapy combination.

Maintenance therapy

One randomized double-blind, placebo-controlled study was identified evaluating the efficacy of topical calcineurin inhibitor maintenance therapy with patients achieving ≥75% or more repigmentation from any treatment modality.

Side effects

Topical calcineurin inhibitor monotherapy:

- Burning sensation, 29/296 (9.8%)
- Pruritus, 22/296 (7.4%)
- Erythema, 7/296 (2.4%)

Limitations

- Heterogeneity in study designs, patient characteristics, and protocols
- Authors stated that the quartile measure is arbitrary but noted that it is the most commonly used measure and currently the best estimate for treatment response
- The meta-analyses were associated with considerable heterogeneity with very high I^2 values of over 90%

Conclusions

Topical calcineurin inhibitor monotherapy showed a favourable response, especially in children and in lesions on the face and neck. Topical calcineurin inhibitors are worth attempting for the treatment of face and neck lesions, particularly in children when phototherapy is not available. Topical calcineurin inhibitors have a synergistic effect when used in combination with phototherapy.

Abbreviations: CI, confidence interval; RCT, randomized controlled trial

Combination

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Chang, H. C., M. H. Lin, et al. (2020). Aesthet Surg J 40(1): NP46-NP50.[17]	Yes	Yes	No – letter, minimal information	Yes	Yes	Within-patient RCTs

Comments

A study to assess the efficacy of fractional CO_2 laser in combination with UVB phototherapy for patients with vitiligo.

Outcomes measures listed match some of those set out in the guideline protocol.

Summary:

Study selection
In total, 53 publications were identified from the search → 27 titles and abstracts were screened → full text publications were assessed for eligibility → 6 studies met the eligibility criteria and were included in quantitative analysis.

Repigmentation (≥ 50%)
A combination of fractional CO_2 laser with UVB was marginally better than UVB monotherapy, but this was not statistically significant.
[6 studies, RR: 1.912; 95% CI (0.736 – 4.968), p=0.184]

Repigmentation (≥ 75%)

A combination of fractional CO_2 laser with UVB was marginally better than UVB monotherapy, but this was not statistically significant.
[5 studies, RR: 1.693; 95% CI (0.496 – 5.775), p=0.400]

Study quality

The risk of bias tool was used to assess the quality of the included studies, none of the studies had a high risk of bias and they were generally of good quality, but, there were some concerns over the methods used for randomization. Publication bias detected in the studies included in the meta-analysis for ≥50% repigmentation and ≥75% repigmentation but this was not statistically significant, p = 0.192 and p = 0.318 respectively.

Limitations

- High heterogeneity existed across the studies
- Some studies utilized topical corticosteroids in both intervention and control groups
- Within-patient RCTs were included in the meta-analyses so this double-counts the number of participants

Conclusions

The meta-analysis did not demonstrate a considerable additional benefit for fractional CO_2 laser in combination with UVB phototherapy.

Abbreviations: CI, confidence interval; CO2, carbon dioxide; UVB, ultra-violet B; RCT, randomized controlled trial

Combination

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
King, Y.-A. (2018). JDDG - Journal of the German Society of	Yes	Yes	No – search strategy not given, only search terms	Yes	Yes	(RCTs, quasi-experimental, within-patient)

Dermatology 16: 1197-1208.[18]						

Comments

A systematic review and meta-analysis to compare the efficacy of vitiligo treatments with and without ablation therapy (erbium laser or CO_2 laser).

Outcome measures listed match some of those set out in the guideline protocol.

Summary:

Study selection

In total, 349 publications were identified from the search → 284 titles and abstracts were screened → 27 full-text publications were screened for eligibility → 15 publications met the eligibility criteria and were included in the systematic review, of these, two studies were not appropriate for quantitative analysis.

The ablation therapy used included erbium-YAG lasers in five studies and CO_2 lasers in 10 studies.

Repigmentation (≥75%)

An ablation-based combination therapy was shown to be better than vitiligo treatment without ablation combination therapy at achieving ≥75% repigmentation [11 studies, OR = 5.812, 95% CI (2.194 – 15.3939), p=0.000]

Repigmentation (≥ 50%)

An ablation-based combination therapy was shown to be better than vitiligo treatment without ablation combination therapy at achieving ≥ 50% repigmentation [11 studies, OR = 10.490, 95% CI (4.632 -23.757), p=0.000]

Sub-group analysis

Inadequately controlled studies were removed from sub-group analysis, these were defined as studies where the differences in therapy between the intervention group and control[1] group were not just ablation therapy but an additional therapy.

[1] In trials investigating CO_2 laser the therapy used in the control group included 5-flurouracil cream, PRP injection, salicylic acid solution, topical corticosteroids and NB-UVB therapy. In trials investigating erbium-YAG laser-based therapy, the therapy used in the control groups included 5-flurouracil, topical corticosteroids, and NB-UVB.

Fractional CO_2 laser combination therapy was shown to be superior to the control group in achieving ≥ 50% regimentation [6 studies, OR=7.810, 95% CI (1.754 – 34.780), p=0.007]

Fractional CO_2 laser combination therapy was shown to be marginally superior to the control group in achieving ≥ 75% repigmentation but the difference was not statistically significant [5 studies, OR =1.897, 95% CI (0.764 – 4.711), p=0.168]

CO_2 laser combination therapy was shown to be superior to the control group in achieving ≥ 50% repigmentation [7 studies, OR=9.964, 95 % CI (3.107–31.955, p<0.001]

CO_2 laser combination therapy was shown to be superior to the control group in achieving ≥ 75% repigmentation, but this was not statistically significant [6 studies, OR=3.901, 95% CI (0.785–19.383), p=0.096]

Non-fractional erbium-YAG laser combination therapy was shown to be superior to the control group in achieving ≥ 50% repigmentation [2 studies, OR = 20.272, 95% CI (1.953 – 210.459), p=0.012] [215,266]

Patient satisfaction score VAS

Seven of the included studies evaluated patient satisfaction. A meta-analysis showed higher satisfaction scores with the ablation-based combination therapy compared with the those receiving vitiligo treatment without ablation therapy [7 studies, SMD: 1.073, 95% CI (0.528 – 1.619), p<0.001].

Side effects

- Pain, burning sensation, erythema, oedema, transient subungual brownish pigmentation, temporary slate-blue pigmentation, oozing, crusting and hypertrophic scars.
- The Koebner phenomenon was not observed in any of the included studies.

Study quality

Study quality was assessed using the Cochrane Collaboration risk of bias tool and the following points were identified:

- Double-blinding was not possible for the included studies as it was not possible for participants to be blinded to laser ablation
- Fifteen of the included studies did not specify the randomization process
- Methods for random sequence generation and allocation concealment were unclear in most of the studies

Limitations

- Statistical heterogeneity was high due to the inclusion of various age groups, vitiligo subtypes, ablation protocols, combination therapies and follow-up times.
- Meta-analysis combined studies of various designs including within-patient studies so this double-counts the number of participants

Conclusions

Ablation-based combination therapy was shown to be a safe and possible more effective treatment for vitiligo than treatment without.

Future research is needed to explore the efficacy of ablation combination therapy in the treatment of various subtypes of vitiligo and to investigate the interaction between ablation therapy and other treatments.

Abbreviations: CI, confidence interval; CO_2, carbon dioxide; OR, odds ratio; RCT, randomized controlled trial; SMD, standardised mean difference; VIAS, visual analogue scale

Light/laser

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Yes/No)	The review collects the type of studies you consider relevant to the guideline review question (Yes/No)	The literature search is sufficiently rigorous to identify all the relevant studies (Yes/No)	Study quality is assessed and reported (Yes/No)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Yes/No)	What types of studies are included in the review? (RCTs/cohort studies/mixed – specify)
Sakhiya, J. J., D. J. Sakhiya, et al. (2019). Journal of Clinical and Diagnostic Research 13(7): WE01-WE11.[19]	Yes	Yes	No – search strategy not given, only search terms	Yes	Yes	RCTs

Comments
A systematic review to compare the efficacy of NB-UVB in combination with topical agents (calcineurin inhibitors, antioxidants, corticosteroids, vitamin – D3 analogues and 5-fluorouracil) or lasers with NB-UVB monotherapy.

Outcome measures listed match some of those outlined in the guideline protocol.

Summary:
Study selection
The search strategy identified 549 publications from the databases → 363 titles and abstracts were screened → 22 full-text publications were assessed → 12 studies met the eligibility criteria.

The included studies investigated the following interventions: antioxidants (n=2), topical calcineurin inhibitors (n= 3), fractional CO_2 laser (n=3), other therapies including ER:YAG laser ablation, dermabrasion, calcipotriol ointment and 5-FU injection (n = 4)

Repigmentation (≥75%)
Antioxidant therapy in combination with NB-UVB was shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentations, but this was not statistically significant [2 studies, RR=1.77, 95% CI (0.93 – 3.35), p=0.08]

Topical calcineurin inhibitors in combination with NB-UVB were shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation [3 studies, [RR=1.79, 95% CI (1.06 - 3.01), p=0.03]

Fractional CO_2 laser in combination with NB-UVB was shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation [2 studies, RR= 7.00 (1.30 - 37.60), p=0.02]
ER: YAG laser ablation and topical 5-FU in combination with NB-UVB was shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation [1 study, RR = 5.60, 95% CI (2.31 - 13.59), p=0.0001]

Dermabrasion in combination with NB-UVB was shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation, but this was not statistically significant [1 study, RR = 5.00, 95% CI (0.26 - 96.59), p=0.29]

5-FU injection in combination with NB-UVB was shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation [1 study, RR=7.25, 95% CI (2.71 - 19.36), p<0.0001]

Calcipotriol ointment in combination with NB-UVB was shown to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation, but this was not statistically significant [1 study, RR=0.67, 95% CI (0.21 - 2.08), p=0.48]

Study quality

- High risk of bias associated with generation (selection bias) in 5/12 studies
- High risk of bias associated with allocation concealment (selection bias) in 5/12 studies
- High risk of bias associated with blinding of participants in 7/12 studies
- High risk of bias associated with blinding of outcome assessors (detection bias) in 8/12 studies
- Incomplete outcome data (attrition bias) in 2/12 studies
- Selective reporting bias (reporting bias) in 3/12 studies
- High risk associated with other biases in 2/12 studies

Limitations

- The use of topical corticosteroids in both groups was acceptable in this systematic review
- Only English language publications were included
- High risk of bias associated with many of the studies
- Small number of studies

Conclusions

The combination of antioxidant or topical calcineurin inhibitors with NB-UVB appear to be superior to NB-UVB monotherapy in achieving ≥75% repigmentation in people with vitiligo.

Abbreviations: 5-FU, flurouracil; CI, confidence interval; CO_2 laser, carbon dioxide laser; NB-UVB, narrow band ultraviolet B; RCT, randomized controlled trial; RR, risk ratio

Summary of main findings from systematic reviews

Table 1: Summary of findings from systematic reviews for topical therapies

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
Repigmentation ≥75%							

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
Steroids	(1) Clobetasol 0.05% > Re-pigmenta, 12 wks.[20] (2) Clobetasol 0.05% > pimecrolimus 1%, 8 wks. (within-patient study design).[81] (3) Clobetasol 0.05% > tacrolimus 0.03%*, 6 mo.[47]	(1) Hydrocortisone 17-butyrate + excimer laser > excimer laser*.[192] (2) Clobetasol propionate > PUVAsol in children *.[212] (3) Fluticasone 0.05% > tacrolimus 0.1%.[267] (4) Mometasone 0.1% > pimecrolimus 1%.[268] (5) Mometasone furoate 0.01% + tacrolimus 0.03% > mometasone furoate 0.01%.[269]	(1) Compared with placebo, topical corticosteroids significantly improved the proportion of patients with >75% repigmentation *****. (2) Fluticasone propionate + UVA > fluticasone propionate ***** (3) Clobetasol propionate > PUVA * at 6mo., in children.	(1) Topical corticosteroid (hydrocortisone 17-butyrate) + excimer laser > excimer laser monotherapy*.[192]			
Vitamin D analogues	(1) PUVA + calcipotriol > calcipotriol*, 6 mo.[54]	(1) Placebo + sunlight > Tacalcitol + sunlight.[270] (2) Calcipotriol + NB-UVB > NB-UVB.[264] (3) Three studies used within-patient study design, but only one study reported sufficient data for analysis; calcipotriol + PUVA > placebo + PUVA.[79]	(1) Calcipotriol + PUVA > PUVA, at achieving complete repigmentation (75-100% repigmentation).	(1) Topical vitamin-D3 analogue + excimer light/laser > excimer laser/light monotherapy*.[193]			

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
Calcineurin inhibitors	(1) Tacrolimus 0.1% + pseudocatalase/superoxide > tacrolimus 0.1%, 9 mos.[56] (2) Tacrolimus 0.1% + microneedling > tacrolimus 0.1%*, 3-mos. post-treatment f/u[59,60] (3) Tacrolimus 0.03% > pimecrolimus 1%[64]	(1) 0.03% tacrolimus > superoxide dismutase + catalase cream.[271] (2) There were some studies which used an intra-participant design, but sufficient data were not reported to allow for appropriate analyses to be conducted.[87,188,190,191,218,261,262,272]		(1) Topical calcineurin inhibitors + excimer laser/light > excimer laser/light monotherapy *. (four studies: RR 1.93, 95% CI 1.28-2.91; NNT 4.5, 95% CI 2.9-10)[188-191].		(1) Tacrolimus + CO_2 > tacrolimus [2 studies, RR 2.11; 95% CI (0.87 – 5.09), p = 0.10][127,273] (2) Tacrolimus vs. steroids, no difference [RR 1.02 (95% CI: 0.19–5.51), P = 0.98][47,100,267,269,272] High heterogeneity between the analysed studies [I^2 = 73%, p = 0.006]	1)Proportional meta-analysis, calineurin inhibitor monotherapy * [19 studies, 18.1%, 95% CI (13.2% - 23.1%), p<0.01] 2)Proportional meta-analysis, calcineurin inhibitor + phototherapy * [nine studies, 47.5%, 95% CI (30.6% - 64.4%), p<0.01] 3)Proportional meta-analysis, calcineurin monotherapy in children, [5 studies, 31.7%, 95% CI (6.7% - 56.8%)] 4) On the face and neck: • Proportional meta analysis, calcineurin

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
							inhibitor monotherapy [16 studies, 35.4 %, 95% CI (24.9% - 46.0%)] • Proportional meta-analysis, calcineurin inhibitor + phototherapy [4 studies, 55.2%, 95% CI (24.6% - 85.9%)] 5) On the trunk and extremities • Proportional meta-analysis, calcineurin inhibitor monotherapy [8 studies, 2.3%, 95% CI (0.3% - 4.3%)] • Proportional meta-analysis, calcineurin inhibitor + phototherapy [3 studies,

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
							16.1%, 95% CI (10.2% - 22.0%)]
Khellin		(1) One study used within-patient design but did not report the data sufficiently to allow for appropriate analyses to be conducted.[274]					
Other	(1) Bioskin > Re-pigmenta*, 12 wks.[20] (2) Re-pigmenta + Bioskin > Re-pigmenta*, 12 wks.[20] (3) Re-pigmenta + Bioskin > Bioskin, 12 wks.[20] (4) Bioskin vs. Clobetasol 0.05%, 12 wks., equivalent.[20] (5) Re-pigmenta + Bioskin > Clobetasol 0.05%, 12 wks.[20] (6) 5-FU + CO_2 > topical 5FU, 6 mo.[23] (7) 5-FU> CO_2, 6 mo.[23] (8) Latanoprost + NB-UVB > NB-UVB *, 6 mo. (within-patient study design).[77]						
Quality of life							

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
Topical corticosteroids		(1) Hydrocortisone 17-butyrate + excimer laser > excimer laser.[192]					
Vitamin D analogues							
Calcineurin inhibitors	(1) Placebo > tacrolimus 0.1%, 6 mo.[21] (2) Tacrolimus 0.1% > placebo emollient *, 12 mo. (within-patient study design).[82]						
Khellin							
Other							
Repigmentation ≥50%							
Corticosteroids	(1) Clobetasol prop. 0.05% > Re-pigmenta, 12 wks. (2) Clobetasol prop. 0.05% > Bioskin, 12 wks.[20] (3) Clobetasol prop. 0.05% > tacrolimus 0.03%*, 6 mo.[47] (4) Betamethasone valerate 0.1% > tacrolimus 0.03%, 3 mo.[48] (5) Betamethasone valerate 0.1% + simvastatin 40mg > betamethasone valerate 0.1%, 12 wks.[46] (6) Tacrolimus 0.1% + Pseudocatalase/superoxide > tacrolimus 0.1%[56] (7) Tacrolimus 0.1% + microneedling > tacrolimus 0.1%[59,60]						

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
	(8) Tacrolimu 0.03% vs. pimecrolimus 1%, no difference[64] (9) bFGF related decapeptide + tacrolimus 0.1% > tacrolimus 0.1%[70]						
Vitamin D analogues							
Calcineurin inhibitors	(1) Tacrolimus 0.03% > clobetasol 0.05%*, 6 mo.[47]					1) Tacrolimus vs. steroids, no difference [5 studies, RR 0.85; 95% CI (0.68 – 1.06), p = 0.15] [47,48,100,267,272]	1) Proportional meta-analysis, calineurin inhibitor monotherapy * [38.5%, 95% CI (28.2% – 48.8%), p<0.01] 2) Proportional meta-analysis, calcineurin inhibitor + phototherapy * [72.9%, 95% CI (57.6% – 88.2%), p< 0.01] 3) Proportional meta-analysis, calcineurin monotherapy in children, [47.3%, 95%

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
							CI (19.0% – 75.7%)] 4) On the face and neck: 4) Proportional meta analysis, calcineurin inhibitor monotherapy [57.5%, 95% CI (44.0% – 70.7%)] 5) Proportional meta-analysis, calcineurin inhibitor + phototherapy 81.5%, 95% CI (10.3% – 92.7%) 5) On the trunk and extremities 6) Proportional meta-analysis, calcineurin inhibitor monotherapy [10.6%, 95% CI (5.3% – 15.8%)] 7) Proportional

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
							meta-analysis, calcineurin inhibitor + phototherapy [44.9%, 95% CI (30.3% – 59.5%)]
Khellin							
Other	(1) Re-pigmenta + Bioskin > Clobetasol, 12 wks.[20] (2) Photocil + sunlight > placebo cream + sunlight, 3 mo.[22] (3) CO_2 laser + topical 5FU > topical 5FU *, 6 mo.[23] (4) Topical 5FU > CO_2 * laser, 6 mo.[23] (5) Clobetasol 0.05% > pimecrolimus 1% *, 8 wks. (within-patient study design).[81]				(1) CO_2 + conventional therapies (topical agents, UVB, sun exposure, and surgery) > conventional therapies (topical agents, UVB, sun exposure, and surgery) alone*[7 studies, OR = 9.964, 95 % CI (3.107–31.955, p<0.001][23,49,90,224,239-241]		
Harms							
Steroids	(1) Betamethasone dipropionate 0.05% + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05%, erythema equivalent at 5 mo.[55] (2) Betamethasone dipropionate 0.05% + calcipotriene 0.005%	Side effects included the following: (1) Folliculitis, mild atrophy, telangiectasia, atrophy, hypertrichosis, or acneiform papules in participants treated with clobetasol propionate.[212,272,275]	Side effects reported included the following: (1) Potent topical corticosteroids – atrophy, corticosteroid-induced acne,				

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
	ointment vs. betamethasone dipropionate 0.05%, scaling, equivalent at 5 mo.[55] (3) Betamethasone dipropionate 0.05% > Betamethasone dipropionate 0.05% + calcipotriene 0.005% ointment, dryness at 5 mo.[55] (4) Betamethasone dipropionate 0.05% + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05%, pruritus, equivalent at 5mo.[55] (5) Betamethasone dipropionate 0.05% > Betamethasone dipropionate 0.05% + calcipotriene 0.005% ointment, burning at 1 mo.[55] (6) Calcipotriene 0.005% > betamethasone 0.05%, erythema at 5 mo.[55] (7) Calcipotriene 0.005% > betamethasone 0.05%, scaling at 5 mo.[55] (8) Calcipotriene 0.005% > betamethasone 0.05%, dryness at 5 mo.[55]	(2) Burning, mild pruritus, dryness, mild erythema, atrophy, telangiectasia and acneiform lesions in participants treated with 0.05% fluticasone propionate.[267] (3) Atrophy, telangiectasia, and erythema in patients treated with mometasone furoate.[268]	and hypertrichosis. (2) Very potent topical corticosteroids – atrophy, telangiectasia, corticosteroid-induced acne, and hypertrichosis.					

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
	(9) Calcipotriene 0.005% > betamethasone 0.05%, pruritus at 5 mo.[55] (10) Calcipotriene 0.005% > betamethasone 0.05%, burning at 1 mo.[55]						
Vitamin D analogues	(1) Calcipotriene 0.005% > Betamethasone dipropionate 0.05% + calcipotriene (0.005%) ointment, erythema at 5 mo.[55] (2) Calcipotriene 0.005% > Betamethasone dipropionate 0.05% + calcipotriene (0.005%) ointment, scaling at 5 mo.[55] (3) Calcipotriene 0.005% > Betamethasone dipropionate 0.05% + calcipotriene (0.005%) ointment, dryness at 5 mo.[55] (4) Calcipotriene 0.005% > Betamethasone dipropionate 0.05% + calcipotriene (0.005%) ointment, pruritus at 5 mo.[55] (5) Calcipotriene 0.005% > Betamethasone dipropionate 0.05% + calcipotriene 0.005% ointment, burning at 1 mo.[55]	Side effects included the following: (1) Mild skin irritation, mild-moderate erythema, dryness, itching and perilesional hyperpigmentation in patients treated with calcipotriol.[79,276] (2) Mild-moderate erythema, drying and itchiness in patients treated with tacalcitol.[193,232,270]	(1) Calcipotriol > betamethasone dipropionate*. (2) Calcipotriol + betamethasone dipropionate > betamethasone dipropionate *. (3) Erythema, itching, irritation, and mild vesiculation associated with calcipotriol treated sides.				

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
	(6) Calcipotriol > calcipotriol + PUVA, erythema at 6 mo.[55] (7) Calcipotriol > calcipotriol + PUVA, pruritus at 6 mo.[55] (8) Calcipotriol > calcipotriol + PUVA, nausea + vomiting at 6 mo.[55]						
Calcineurin inhibitors	Side effects included the following: (1) Transient facial flushing, enhanced heat intolerance, burning, mild pruritus, and mild perioral folliculitis in patients treated with tacrolimus at 12 mo.; these did not lead to discontinuation of therapy (within-patient study design).[82] (2) Transient pruritus at 7 mo.; otherwise, it was well tolerated (within-patient study design).[85] (3) Atrophy, atrophy, telangiectasia and acneiform changes were observed in patients using	Side effects included the following: (1) Burning sensation, papules, erythema, mild pruritus, atrophy and pyoderma in patients treated with tacrolimus.[267,271,272] (2) Soreness, erythema, burning, intense lachrymation in patients treated with pimecrolimus.[268,277]					

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]	Bae, J.M. 2016[4]	Kim, H.J. 2018[12]	Arora, C.J. 2020[15]	Lee, J. H., H. S. (2019) [16]
	pimecrolimus 1% at 8 wks. (within-patient study design).[81]						
Khellin							
Other							

* indicates a statistically significant result (p<0.05).

Abbreviations: 5FU, 5-flurouracil; CO_2, carbon dioxide; CI, confidence interval; mo., month; NNT, number needed to treat; NB-UVB, narrow band ultraviolet B; PUVA, psoralens and ultraviolet A; PUVAsol, psoralens + ultraviolet A + sunlight; RR, risk ratio; wks, weeks

> denotes the intervention is better than the comparator for the outcome of interest

Table 2: Summary of findings from systematic reviews for systemic therapies

Intervention	Our findings	Whitton, M.E. 2015[2]	Matin, R. 2011[3]
Repigmentation ≥75%			
Steroids	(1) Minocycline > OMP dexamethasone, 6 mo.[24]	(1) OMP betamethasone + NB-UVB > OMP betamethasone *.[168] (2) OMP betamethasone + PUVA > OMP betamethasone.[168]	
Other		(1) Azathioprine + PUVA > PUVA*.[169] (2) Antioxidant pool (alpha lipoic acid, vitamin C and E and fatty acids) + NB-UVB > NB-UVB*.[174]	
Quality of life			
Steroids			
Other		(1) Oral levamisole + topical mometasone furoate vs. placebo + topical mometasone, DLQI, no significant difference seen between the two.[170]	No RCTs were identified; the author concluded that the effectiveness of oral levamisole is unknown.
Repigmentation ≥50%			
Steroids			
Other			
Harms			
Steroids	(1) Minocycline > OMP dexamethasone, 6 mo.[24]		
Other	(1) Methotrexate > OMP dexamethasone, 6 mo.[25]		

* indicates a statistically significant result (p<0.05).

Abbreviations: DLQI, dermatology life quality index; mo., month; NB-UVB, narrow band ultraviolet B; OMP, oral minipulse; PUVA, psoralens + ultraviolet A.

> denotes the intervention is better than the comparator for the outcome of interest

Table 3: Summary of findings from systematic reviews for light and laser therapies

Intervention	Our findings	Arora, C. J. (2020).	Bae, J.M. 2016[4]	Chang, H. C. 2020	Chiu 2018[9]	Jin, J. 2016[14]	King, Y.-A. (2018).	Li, R. 2017[10]
Repigmentation ≥75%								
Excimer light/ laser	(1) Hand-held, home-based phototherapy (HBP) > Institution-based excimer lamp (IBEL), 6 mo.[32] (2) PRP + excimer laser > excimer laser*, 3 mo. post-treatment[65] (3) Tacrolimus 0.1% + excimer laser > excimer laser (p = 0.05), complete repigmentation (in children) at 12 wks.[68] (4) Pimecrolimus 1% + excimer laser > excimer laser, complete repigmentation at 12 wks.[68] (5) Halometasone + excimer lase > excimer laser, complete repigmentation (in children)*at 12 wks.[68] (6) Halometasone + excimer laser > excimer laser, complete repigmentation*[67]	(1) Excimer laser + tacrolimus > excimer laser [2 studies, RR 2.39; 95% CI (0.64 – 8.96), p = 0.20][189,190]	(1) Topical vitamin-D3 analogue + excimer light/laser > excimer laser/light monotherapy *.[193] (2) Topical corticosteroid (hydrocortisone 17-butyrate) + excimer laser > excimer laser *.[192] (3) Topical calcineurin inhibitors + excimer laser/light > excimer laser/light monotherapy *[188-191]			(1) excimer laser/light alone < excimer light/laser + topical therapy (tacalcitol, calcipotriol, hydrocortisone, pimecrolimus, and tacrolimus) *(five studies: RR= 0.45, 95% CI: 0.32 – 0.65, p<0.05).[188-190,192,193]		

	(7) Tacrolimus 0.1% + excimer laser > excimer laser[67]							
PUVA	(1) Oral PUVA > PUVA sol, 36 wks.[31] (2) Calcipotriol + PUVA > placebo + PUVA, 8 wks.[79] (within-patient study design)							
NB-UVB	(1) Hand-held NB-UVB > placebo device, 16 wks.[27] (2) NB-UVB + Vitix gel > NB-UVB, 6 mo.[34] (3) NB-UVB + intradermal injection of platelet rich plasma (PRP) > NB-UVB, 3 mo.[95] (within-patient study design). (4) NB-UVB + micro-needling + topical triamcinolone > NB-UVB, 5 mo.[62] (5) Home-based NB-UVB > hospital-based NB-UVB, 3 mo.[69] (6) Vitilinex + NB-UVB > NB-UVB (7) Outpatient NB-UVB > home-based NB-UVB[74]	(1) Tacrolimus + NB-UVB > NB-UVB*[2 studies, RR 1.34; 95% CI (1.05 – 1.71), p = 0.02][52,265]		(1) CO_2 + NB-UVB > NB-UVB [5 studies, RR: 1.693; 95% CI (0.496 – 5.775), p = 0.400][90,118,121,122,241]				(1) NB-UVB + calcineurin inhibitors > NB-UVB (two studies: RR= 1.84, 95% 0.90-3.78, p =0.09).[175,262] (2) NB-UVB + vitamin D3 analogs > NB-UVB (1 study: RR = 0.67, 95% CI 0.21, 2.08, p=0.48).[109]

Laser – other	(1) Topical 5FU + CO2 > CO2*, 6 mo.[23] (2) Topical 5FU > CO2, 6 mo.[23] (3) CO_2 laser alone > CO_2 laser + NB-UVB, 5 mo.[49] (4) CO_2 laser + PRP > CO_2 laser, 5 mo.[49] (5) PRP > CO_2 laser[49]				(1) Adjunct CO_2 laser > no adjunct CO_2 laser* (six studies: RR, 2.80; 95% CI:1.29 – 6.07, p = 0.009)[90,224,239-242]		(1) Ablation laser therapies (erbium-YAG resurfacing/ablative CO_2 laser) combination therapy* > monotherapy [11 studies, OR = 5.812, 95% CI (2.194 – 15.3939), p = 0.000][23,49,90,215{Shin, 2012 #160,239-242,224,266,278 (2) Fractional CO_2 combination therapy > monotherapy [5 studies, OR =1.897, 95% CI (0.764 – 4.711), p = 0.168][49,90,239-241 (3) CO_2 combination> monotherapy [6 studies, OR = 3.901, 95% CI (0.785–19.383), p = 0.096][23,49,90,239-241	

Light – other	(1) Tacrolimus 0.1% + Bioskin > Bioskin, 6 mo.[30] (2) Pimecrolimus 1% + Bioskin > Bioskin, 6 mo.[30] (3)Betamethasone dipropionate 0.05% + Bioskin > Bioskin *, 6 mo.[30] (4) Bioskin = calcipotriol ointment 50 µg/g + Bioskin, 6 mo.[30] (5) Bioskin = 10% L-phenylalanine + Bioskin, 6 mo.[30] (6) Bioskin > tacrolimus 0.1%, 6 mo.[30] (7) Bioskin > pimecrolimus 1%, 6 mo.[30] (8) Betamethasone dipropionate 0.05% = Bioskin, 6 mo.[30] (9) Bioskin > calcipotriol, 6 mo.[30]. (10) Bioskin > L-phenylalanine 10%*, 6 mo.[30]								
Quality of life									
Excimer light/laser	(1) yiqiqubai granules + excimer laser > excimer laser for: Embarrassment*, Dress, Social*, and								

	Work* subcategories.[53] (2) Yiqiqubai granules + excimer laser > yiqiqubai granules for: Embarrassment*, Dress, Social*, and Work* sub-categories.[53]							
PUVA	(1) Oral PUVA was associated with better QoL at 36 wks. Compared with PUVA sol *.[31]							
NB-UVB	(1) Hand held NB-UVB therapy was associated with a decline in DLQI but this was not statistically significant. (2) OCG + NB-UVB > NB-UVB, 6 mo.[50] (3) Home based NB-UVB > outpatient NB-UVB, 6 mo.[74]							
Laser – other								
Light – other								
Repigmentation ≥50%								

Excimer light/laser	(1) Hand-held HBP > Institution-based excimer lamp (IBEL), 6 mo.[32] (2) Calcipotriol + PUVA > PUVA, 15 wks. (within-patient study design).[93] (3) Yiqiqubai granules + excimer laser > yiqiqubai granules*.[53] (4) yiqiqubai granules + excimer laser > excimer laser.[53] (5) Halometasone + excimer laser > excimer laser (in children), 12 wk.[68] (6) Halometasone + excimer laser > excimer laser, 12 wk.[67] (7) Tacrolimus 0.1% + excimer laser > excimer laser*, 12 wk.[67] (8) Tacrolimus 0.1% + excimer laser > excimer laser (in children), 12 wk.[68] (9) Pimecrolimus + excimer laser > excimer laser (in children)[68] (10) PRP + excimer laser > excimer laser*, 3 mo. post-treatment[65]	1) Tacrolimus + excimer laser > excimer laser [2 studies, RR 2.11; 95% CI (0.87 – 5.09), p = 0.10] [127,273]				(1) excimer laser/light alone < excimer light/laser + topical therapy (tacalcitol, calcipotriol, hydrocortisone, pimecrolimus, and tacrolimus) (four studies: RR= 0.98, 95% CI: 0.64 – 1.51)[188-190,193]		

PUVA	(1) Oral PUVA > PUVA sol, 36 wks.[31]							
NB-UVB	(1) NB-UVB > PUVA, 6 mo.[26] (2) NB-UVB + VitE > NB-UVB, 6 mo.[28] (3) NB-UVB + Vitix gel > NB-UVB, 6 mo.[34] (4) NB-UVB + intradermal injection of platelet rich plasma > NB-UVB, 3 mo.[95] (5) NB-UVB + micro-needling + topical triamcinolone > NB-UVB*, 5 mo.[62] (6) Vitilinex + NB-UVB > NB-UVB, 12 wks.[73]			(1) CO_2 + NB-UVB > NB-UVB [6 studies, RR: 1.912; 95% CI (0.736 – 4.968), p = 0.184] [90,118,121,122,224,241]				(1) NB-UVB + calcineurin inhibitors > NB-UVB alone (three studies: RR = 1.22, 95% CI: 0.88 – 1.68), p = 0.23) (2) NB-UVB + topical vitamin D3 > NB-UVB alone (three studies: RR = 1.50, 95% CI: 0.75 – 2.99, p=0.25)
Laser – other	(1) Topical 5-FU + CO_2 > CO_2*, 6 mo.[23] (2) Topical 5-FU > CO_2 laser, 6 mo.[23]				(1) Adjunct CO_2 laser > no adjunct CO_2 laser* (six studies: RR, 2.62; 95% CI: 1.58 – 4.34, p = 0.0002)[90,224,239-242]		(1) Ablation laser therapies (erbium-YAG resurfacing/ablative CO_2 laser) combination therapy > monotherapy*[11 studies, OR = 10.490, 95% CI (4.632 - 23.757), p = 0.000] [23,49,90,215,224,239-242,266,278] (2) Fractional CO_2 laser	

							combination therapy > monotherapy* [6 studies, OR = 7.810, 95% CI (1.754 – 34.780), p = 0.007][49,90,224,239-241] (3) Non-fractional erbium-YAG laser combination > monotherapy* [2 studies, OR = 20.272, 95% CI (1.953 – 210.459), p = 0.012][215,266]	
Light – other	(1) Tacrolimus 0.1% + Bioskin[2] > Bioskin, 6 mo.[30] (2) Pimecrolimus 1% + Bioskin > Bioskin, 6 mo.[30] (3) Betamethasone dipropionate 0.05% + Bioskin > Bioskin, 6 mo.[30] (4) Bioskin = calcipotriol ointment 50 µg/g + Bioskin, 6 mo.[30] (5) Bioskin = calcipotriol ointment							

[2] 311- nm narrow-band micro-phototherapy

	50 µg/g + Bioskin, 6 mo.[30] (6) Bioskin = 10% L-phenylalanine + Bioskin, 6 mo.,[30] (7) Bioskin > tacrolimus 0.1%, 6 mo.[30]. (8) Bioskin > pimecrolimus 1%, 6 mo.[30] (9) Betamethasone dipropionate 0.05% > Bioskin, 6 mo.[30] (10) Bioskin > calcipotriol, 6 mo.[30] (11) Bioskin > L-phenylalanine 10%*, 6 mo.[30] (12) Khellin 2% + sunlight > placebo + sunlight, 4 mo. (within-patient study design).[96] (13) Khellin + water/2-propanol/propylene1 % Glycol + UVA > placebo + UVA, 6 mo. (within-patient study design).[97]								
Harms									
Excimer light/laser	(1) Erythema and hyperpigmentation (within-patient study design).[92]					(1) excimer laser/light alone < excimer light/laser + topical therapy (tacalcitol, calcipotriol,			

						hydrocortisone, pimecrolimus, and tacrolimus) (four studies: RR=0.70, 95% CI: 0.37 – 1.31).[188,189,192,193]		
PUVA								
NB-UVB	(1) Hand-held NB-UVB side effects: Pruritus, hyperpigmentation around the lesions and dry skin, erythema, cold sores.[27] (2) NB-UVB + VitE > NB-UVB, 6 mo., mild erythema.[28] (3) NB-UVB > Afamelanotide implant (four times a mo.) + NB-UVB, 6 mo., side effects.[29] (4) Outpatient NB-UVB > home-based NB-UVB, painful erythema, 6 mo.[74] (5) Outpatient NB-UVB > home-based NB-UVB, 6 mo., skin burning[74]							

Laser – other	(1) Patients receiving CO_2 laser + 5-FU topical cream combination or CO_2 laser monotherapy experienced more frequent side effects as compared with patients receiving 5-FU topical cream alone. This was not statistically significant except for transient hyperpigmentation *.				(1) The most common side effect was pain, followed by burning sensation, erythema, oedema, and oozing. No infection, scarring, or Koebner phenomenon occurred after using fractional CO_2 laser.			
Light – other								

* indicates a statistically significant result (p<0.05)

Abbreviations: 5-FU, fluorouracil; 8-MOP, methoxypsoralen; CO_2, carbon dioxide; DLQI, dermatology life quality index; HBP, home-based phototherapy; IBEL, institution-based excimer lamp; mo., month; NB-UVB, narrow band ultraviolet B; OMP, oral minipulse; QoL, quality of life; RR, risk ratio; TMP, trimethylpsoralen; UVA, ultraviolet A; vitE, vitamin E; yr., year.

> denotes the intervention is better than the comparator for the outcome of interest

Table 4: Summary of light and laser therapies cont'd

Intervention	Our findings	Matin, R. 2011[3]	Sun, Y. 2015[5]	Sakhiya, J.J. 2019	Whitton, M.E. 2015[2]	Xiao, B.H. 2015[6]
Repigmentation ≥75%						
Excimer light/ laser	(1) Hand-held, home-based phototherapy (HBP) > Institution-based excimer lamp (IBEL), 6 mo.[32] (2) PRP + excimer laser > excimer laser*, 3 mo. post-treatment[65] (3) Tacrolimus 0.1% + excimer laser > excimer laser (p =		(1) A meta-analysis under the fixed effects showed that there was no statistically significant difference between 308nm excimer laser and lamp (lesions).		(1) Monochromatic excimer light vs. NB-UVB, > 75% repigmentation was observed in both groups; the study was not reported in a suitable way to enable appropriate analyses to be conducted. (Within-	

	0.05), complete repigmentation (in children) at 12 wks.[68] (4) Pimecrolimus 1% + excimer laser > excimer laser, complete repigmentation at 12 wks.[68] (5) Halometasone + excimer lase > excimer laser, complete repigmentation (in children)*at 12 wks.[68] (6) Halometasone + excimer laser > excimer laser, complete repigmentation*[67] (7) Tacrolimus 0.1% + excimer laser > excimer laser[67]				patient study design) (2) 308nm excimer laser vs. 308 nm excimer lamp, > 75% repigmentation was observed in both groups; the study was not reported in a suitable way to enable appropriate analyses to be conducted. (Within-patient study design) (3) Hydrocortisone 17-butyrate + excimer laser > excimer laser *.[192]	
PUVA	(1) Oral PUVA > PUVA sol, 36 wks.[31] (2) Calcipotriol + PUVA > placebo + PUVA, 8 wks.[79] (within-patient study design)				(1) Meta-analysis found a non-statistically significant 60% increase in the proportion of patients achieving > 75% repigmentation in favour of NB-UVB compared with oral PUVA.[173,229,230] (2) OMP betamethasone + PUVA > OMP betamethasone.[168]	(1) Two trials compared NB-UVB with PUVA, meta-analysis showed no statistically significant difference between the two treatments on the number of patients who achieved >50% repigmentation.[168,229]

NB-UVB	(1) Hand-held NB-UVB > placebo device, 16 wks. [27] (2) NB-UVB + Vitix gel > NB-UVB, 6 mo.[34] (3) NB-UVB + intradermal injection of platelet rich plasma (PRP) > NB-UVB, 3 mo.(within-patient study design). [95] (4) NB-UVB + micro-needling + topical triamcinolone > NB-UVB, 5 mo.[62] .[62] (5) Home-based NB-UVB > hospital-based NB-UVB, 3 mo.[69] (6) Vitilinex + NB-UVB > NB-UVB[73] (8) Outpatient NB-UVB > home-based NB-UVB[74]		(1) Meta-analysis under the fixed effects showed that there was no statistically significant difference between 308nm excimer laser and NB-UVB (for both lesions and patients).	(1) Antioxidant + NB-UVB > NB-VB [2 studies, RR = 1.77, 95% CI (0.93 – 3.35), p = 0.08] [174] Li 2016] (2) ER:YAG laser + topical 5-FU + NB-UVB > NB-UVB* [1 study, RR = 5.60, 95% CI (2.31 - 13.59), p = 0.0001][215] (3) Fractional CO_2 + NB-UVB > NB-UVB* [2 studies, RR = 7.00 (1.30 - 37.60), p = 0.02] [90,118,224] (4) 5-FU injection + NB-UVB > NB-UVB* [1 study, RR = 7.25, 95% CI (2.71 - 19.36), p < 0.0001][91] (5) Calcipotriol + NB-UVB > NB-UVB [1 study, RR = 0.67, 95% CI (0.21 - 2.08), p = 0.48][109] (6) Calcineurin + NB-UVB > NB-UVB* [3 studies, RR = 1.79, 95% CI (1.06 - 3.01), p = 0.03][175,262,265]	(1) Antioxidant pool (alpha lipoic acid, vitamin C and E and fatty acids) + NB-UVB > NB-UVB*.[174] (2) OMP betamethasone + NB-UVB > OMP betamethasone *.[168] (3) pimecrolimus + NB-UVB > placebo + NB-UVB.[175] (4) NB-UVB + vitamin E > NB-UVB.[28]	
Laser – other	(1) Topical 5FU + CO2 > CO2*, 6 mo.[23]					

	(2) Topical 5FU > CO2, 6 mo.[23] (3) CO_2 laser alone > CO_2 laser + NB-UVB, 5 mo.[49] (4) CO_2 laser + PRP > CO_2 laser, 5 mo.[49] (5) PRP > CO_2 laser[49]					
Light – other	(1) Tacrolimus 0.1% + Bioskin > Bioskin, 6 mo.[30] (2)Pimecrolimus 1% + Bioskin > Bioskin, 6 mo.[30] (3)Betamethasone dipropionate 0.05% + Bioskin > Bioskin *, 6 mo.[30] (4) Bioskin = calcipotriol ointment 50 µg/g + Bioskin, 6 mo.[30] (5) Bioskin = 10% L-phenylalanine + Bioskin, 6 mo.[30] (6) Bioskin > tacrolimus 0.1%, 6 mo.[30] (7) Bioskin > pimecrolimus 1%, 6 mo.[30] (8)Betamethasone dipropionate 0.05% = Bioskin, 6 mo.[30] (9) Bioskin > calcipotriol, 6 mo.[30]. (10) Bioskin > L-	(1) Trioxysalen + UVA may be more effective than UVA alone at 2 yrs. in adults and children.			(1) 8-MOP > psoralens*.[214] (2) 8-MOP + TMP > psoralens *.[214] (3) placebo > TMP.[279]	

	phenylalanine 10%*, 6 mo.[30]					
Quality of life						
Excimer light/laser	(1) yiqiqubai granules + excimer laser > excimer laser for: Embarrassmen*, Dress, Social*, and Work* subcategories.[53] (2) Yiqiqubai granules + excimer laser > yiqiqubai granules for: Embarrassment*, Dress, Social*, and Work* sub-categories.[53]				(1)Hydrocortisone 17-butyrate + excimer laser > excimer laser.[192]	
PUVA	(1) Oral PUVA was associated with better QoL at 36 wks. Compared with PUVA sol*.[31]				(1) One study measured DLQI, at 1 yr. follow-up, showing a reduction in DLQI, but the results were not statistically significant.[173]	
NB-UVB	(1) Hand held NB-UVB therapy was					

	associated with a decline in DLQI but this was not statistically significant. (2) OCG + NB-UVB > NB-UVB, 6 mo.[50]					
Laser – other						
Light – other						
Repigmentation ≥50%						
Excimer light/laser	(1) Hand-held HBP> Institution-based excimer lamp (IBEL), 6 mo.[32] (2) Calcipotriol + PUVA > PUVA, 15 wks. (within-patient study design).[93] (3) Yiqiqubai granules + excimer laser > yiqiqubai granules*.[53] (4) yiqiqubai granules + excimer laser > excimer laser.[53] (5) Halometasone + excimer laser > excimer laser (in children), 12 wk.[68] (6) Halometasone + excimer laser > excimer laser, 12 wk.[67] (7) Tacrolimus 0.1% + excimer laser > excimer laser*, 12 wk.[67] (8) Tacrolimus 0.1% + excimer laser >		(1) Meta-analysis under the fixed effects showed that there was no statistically significant difference between 308nm excimer laser and lamp (lesions).			

	excimer laser (in children), 12 wk.[68] (9) Pimecrolimus + excimer laser > excimer laser (in children)[68] (10) PRP + excimer laser > excimer laser*, 3 mo. post-treatment[65]					
PUVA	(1) Oral PUVA > PUVA sol, 36 wks.[31]	(1) Oral PUVA may be no more effective at 18 mo. than topical PUVA. (2) Compared to no treatment, topical PUVA is no more effective at 18 mo.				(1) Two trials compared NB-UVB with PUVA, meta-analysis showed no statistically significant difference between the two treatments on the number of patients who achieved >50% repigmentation[168,229]
NB-UVB	(1) NB-UVB > PUVA, 6 mo.[26] (2) NB-UVB + VitE > NB-UVB, 6 mo.[28] (3) NB-UVB + Vitix gel > NB-UVB, 6 mo.[34] (4) NB-UVB + intradermal injection of platelet rich plasma > NB-UVB, 3 mo.[95] (5) NB-UVB + micro-needling + topical triamcinolone > NB-UVB*, 5 mo.[62] (5) Vitilinex + NB-UVB > NB-UVB, 12 wks.[73]	(1) It is not clear how effective oral PUVA and UVB are compared with each other at improving repigmentation rates in adults.	(1) Meta-analysis showed that more patients (two studies: RR 1.39, 95% CI 1.05-1.85; p = 0.002)[233,234] or lesions (one study: RR 1.41, 95% CI 1.09-1.82; p = 0.009)[233] achieved ≥50% repigmentation rate by 308nm excimer laser than by NB-UVB treatment*.			(1) Two trials compared NB-UVB with UVA control, meta-analysis showed no statistically significant difference between the two methods on the number of patients who achieved > 60% repigmentation.[235,236]
Laser – other	(1) Topical 5-FU + CO_2 > CO_2*, 6 mo.[23]					

	(2) Topical 5-FU > CO_2 laser, 6 mo.[23]					
Light – other	(1) Tacrolimus 0.1% + Bioskin[3] > Bioskin, 6 mo.[30] (2) Pimecrolimus 1% + Bioskin > Bioskin, 6 mo.[30] (3)Betamethasone dipropionate 0.05% + Bioskin > Bioskin, 6 mo.[30] (4) Bioskin = calcipotriol ointment 50 µg/g + Bioskin, 6 mo.[30] (5) Bioskin = calcipotriol ointment 50 µg/g + Bioskin, 6 mo.[30] (6) Bioskin = 10% L-phenylalanine + Bioskin, 6 mo.,[30]. (7) Bioskin > tacrolimus 0.1%, 6 mo.[30]. (8) Bioskin > pimecrolimus 1%, 6 mo.[30]. (9) Betamethasone dipropionate 0.05% > Bioskin, 6 mo.[30]. (10) Bioskin > calcipotriol, 6 mo.[30]. (11) Bioskin > L-phenylalanine 10%*, 6					

[3] 311- nm narrow-band micro-phototherapy

	mo.[30]. (12) Khellin 2% + sunlight > placebo + sunlight, 4 mo. (within-patient study design).[96] (13) Khellin + water/2-propanol/propylene1 % Glycol + UVA > placebo + UVA, 6 mo. (within-patient study design).[97]					
Harms						
Excimer light/laser	(1) Erythema and hyperpigmentation (within-patient study design).[92]		(1) Erythema, itching, pain, burning, and blistering.[233,234,280,281]		(1) Burning, stinging, moderate-severe erythema, oedema, and blisters.[282] (2) Burning and Blisters.[188]	
PUVA					(1) In a meta-analysis, NB-UVB > oral PUVA, nausea * (RR 0.13, 95%CI 0.02 to 0.69) and erythema * (RR 0.73, 95%CI 0.55 to 0.98); itching (RR 0.57, 95%CI 0.20 to 1.60).[173,229,230] (2) OMP + PUVA: perilesional hyperpigmentation, excessive erythema, weight gain.[168]	
NB-UVB	(1) Hand-held NB-UVB side effects:				(1) Perilesional pigmentation and	(1) Erythema, mild burning or pain, mild-moderate itching. These

	Pruritus, hyperpigmentation around the lesions and dry skin, erythema, cold sores.[27] (2) NB-UVB + VitE > NB-UVB, 6 mo., mild erythema.[28] (3) NB-UVB > Afamelanotide implant (four times a mo.) + NB-UVB, 6 mo., side effects.[29] (4) Outpatient NB-UVB > home-based NB-UVB, painful erythema, 6 mo.[74] (5) Outpatient NB-UVB > home-based NB-UVB, 6 mo., skin burning[74]				mild-moderate erythema.[176]	were reported to be well-tolerated by most patients and generally disappeared several hours after treatment.
Laser – other	(1) Patients receiving CO_2 laser + 5-FU topical cream combination or CO_2 laser monotherapy experienced more frequent side effects as compared with patients receiving 5-FU topical cream alone. This was not statistically significant except for transient hyperpigmentation*.					
Light – other					(1) Nausea, pruritus, dizziness, headaches, eye discomfort, and	

					vague gastrointestinal symptoms.[214] (2) Mild atrophy in patients treated with UVA and UVA + fluticasone propionate combination.[88]	

Abbreviations: CI, confidence interval; CO_2 , carbon dioxide; HBP, home-based phototherapy; IBEL, institution-based excimer lamp; NB-UVB, narrow band ultraviolet B; OCG, oral glyrcyrrhizin; OMP, oral minipulse; UVA, ultraviolet A.

* indicates a statistically significant result ($p<0.05$)

> denotes the intervention is better than the comparator for the outcome of interest

Table 5: Summary of findings from systematic reviews for surgical therapies

Intervention	Our findings	Whitton, M.E. 2015[2]
Repigmentation ≥75%		
Suction blister grafts		(1) One study used a within-patient study design, it did not report data suitably to allow for an appropriate analysis to be conducted.[216]
Punch grafts, minigrafts and split thickness skin grafts	(1) UTSG>MPG, 6 mo.[39]	(1) Minipunch grafting + PUVAsol > splitskin + PUVAsol *.[213]. (2) NCES > NCORSHFS.[222]
Melanocyte transplantation	(1) NCES >UTSG, 6 mo.[39] (2) NCES > MPG, 6 mo.[39] (3) BG > CMT *, (≥90% repigmentation), 12 mo., (within-patient study design).[98] BG > NCES *, (≥90% repigmentation), 12 mo., (within-patient study design).[98] (4) CMT > NCES, (≥90% repigmentation), 12 mo., (within-patient study design).[98] (5) ECS > FCS*, 16 wks.[107] (6) ECS > FCS* (≥90% repigmentation), 16 wks.[107] (7) NCES/NDCS > NCES*, 24-wks. post-treatment[72]	(1) Melanocytes suspended in patient's own serum>Melanocytes suspended in normal saline.[195]
Microneedling	(1) Microneedling + tacrolimus 0.1% > microneedling*, 3 mo. post-treatment[59] (2) Microneedling + NB-UVB > microneedling, 3 mo.[62]	

Intervention	Our findings		Whitton, M.E. 2015[2]
Hair follicle extraction	(1) NCORSHFS > NCES, 3 mo.[63] (2) FUE > PHF, 16-wk.[72]		
Quality of life			
Suction blister grafts			
Punch grafts, minigrafts and split thickness skin grafts			In both NCES and NCORSHFS there was a significant reduction in DLQI * but the decline was not statistically significant between the two groups.[222]
Melanocyte transplantation			A significant reduction in DLQI was found in both groups * and significantly better when melanocytes were suspended in the participant's own serum*.[195]
Hair follicle extraction			
Repigmentation ≥50%			
Suction blister grafts			
Punch grafts, minigrafts and split thickness skin grafts	(1) UTSG = MPG, 6 mo.[39] (2) NCES > UTSG, 6 mo.[39] (3) MPG vs., NCES, equivalent, 6 mo.[39]		
Melanocyte transplantation	(1) NCES/NDCS > NCES*, 24 wk. post-treatment f/u[72]		
Microneedling	(1) Microneedling + tacrolimus 0.1% > microneedling*, 3 mo. post-treatment[59] (2) Microneedling + triamcinolone 10mg/mL+ NB-UVB > microneedling, 3 mo.[62]		
Hair follicle extraction	(1) FUE > PHF, 16-wk. post treatment[71]		
Harms			
Suction blister grafts		The side effects did not differ significantly between the groups, the most common was perigraft halo. Other side effects were hyperpigmentation,	(1) Suction blister graft vs. thin split thickness graft - Koebner phenomenon and papules were the most common, other side effects were, hypopigmentation, hyperpigmentation, scarring, and infection at the donor site, pigment loss.[221]

Intervention	Our findings		Whitton, M.E. 2015[2]
Punch grafts, minigrafts and split thickness skin grafts	(1) 1.5mm deep punch grafts were associated with greater erythema compared with 1.00 or 1.50 superficial punch grafts and 1.00mm deep punch grafts* and greater hypopigmentation than 1.00 superficial punch grafts.[106] (2) Hyperpigmentation, NCES + Thiersch graft > NCES +blister roof graft*[57]	graft dislodgement, cobblestoning, textural irregularity and infection.	(1) Cobblestoning, superficial scarring (all participants), and variegated appearance were observed in in the punch grafting group.[213]
Melanocyte transplantation			(1) Halo phenomenon and hyperpigmentation were observed in both groups; however, scarring was only observed in participants whose melanocytes were suspended in normal saline.[195]
Microneedling	(1) Microneedling > Microneedling + tacrolimus 0.1%, erythema[59] (2) Microneedling + tacrolimus 0.1% > microneedling, pain[59]		
Hair follicle extraction	(1) NCORSHFS > NCES, hyperpigmentation[63] (2) NCORSHFS > NCES, mild scarring[63]		

Abbreviations: BG, blister roof graft; CMT, cultured melanocyte transplantation; DLQI, dermatological life quality index; ECS, epidermal cell suspension; FCS, follicular cell suspension; MPG, miniature punch graft; NCES, nonculture epidermal cell suspension technique; NCORSHFS, non-cultured extracted hair follicle outer root sheath cell suspension; UTSG, ultra-thin skin graft.

* indicates a statistically significant result ($p<0.05$)

> denotes the intervention is better than the comparator for the outcome of interest

Table 6: Summary of findings from systematic reviews for psychological therapies

Intervention	Our findings	Whitton, M.E. 2015[2]
Quality of life		

Cognitive behavioural therapy		(1) Participants receiving CBT and PCT showed significant improvements in their responses to the General Health Questionnaire up to 12 mos. after therapy.[43]
Patient centred therapy		
Cognitive behavioural self-help	bFNE score:(1) A higher percentage of participants showed RCS[4] in the CBSH+[5] group (24%) than in the other two groups (8% in the CBSH group and 0% in the control group).[44]	
Other		

Abbreviations: bFnE, brief fear of negative evaluation scale; CBSH, Cognitive behavioural self-help; CBSH+, Cognitive behavioural self-help enhanced; CBT, cognitive behavioural therapy; PCT, person-centred therapy; RCS, reliable and clinically significant improvement

* indicates a statistically significant result ($p<0.05$)

> denotes the intervention is better than the comparator for the outcome of interest

Table 7:Summary of findings from systematic reviews for skin camouflage therapies

Intervention	Our findings
Quality of life	
Skin camouflage	(1) Patients receiving a camouflage sample matching their skin complexion were followed up after at least 1 mo., DLQI scores improved after camouflage use *.[199] (2) Patients receiving skin camouflage lessons showed an improvement in DLQI scores but those without skin camouflage lessons showed a worsening in DLQI scores after 1 mo. of bimonthly lessons *.[45] (3) Children receiving camouflage therapy showed an improvement in cDLQI scores 2 wks. after the workshop.[137] (4) Patients using DHA for skin camouflage were dissatisfied with the product due to irregular brownish staining and no staining at all.[138]

Abbreviations: cDLQI, children dermatology life quality index; DHA, dihydroxyacetone; DLQI, dermatology life quality index; wks., weeks.

* indicates a statistically significant result ($p<0.05$)

Table 8:Summary of findings from systematic reviews for complementary therapies

Intervention	Our findings	Whitton, M.E. 2015[2]	Chen, Y.J., 2016[7]
Repigmentation ≥75%			
Ginkgo Biloba		Ginkgo biloba > placebo *.[200]	
Pseudocatalase and catalase/dismutase superoxide		(1) NB-UVB + pseudocatalase vs. placebo, collected data on patients achieving >90% repigmentation;	

[4] If scores were more than the clinically significant value, then they were classified as a reliable and clinically significant improvement.

[5] CBSH augmented with implementation intentions, this provided specific if-then plans aimed at increasing the use of the interventions. For example, how to respond to feeling anxious at a party or whilst shopping.

Intervention	Our findings	Whitton, M.E. 2015[2]	Chen, Y.J., 2016[7]
		the data was not reported in a way that would enable an analysis of >75% repigmentation.[283] (2) One study compared a gel containing pseudocatalase and superoxide with placebo, but repigmentation was reported as "partial" or "complete".[284]	
Tetrahydrocurcuminoid cream		(1) Tetrahydrocurcuminoid + NB-UVB vs. NB-UVB, data presented as mean repigmentation scores, no participants achieved >75% repigmentation.	
Oral L-phenylalanine		(1) L-phenylalanine + UVA > no active treatment.[250] (2) L-phenylalanine > no active treatment.[250]	
Chinese herbal medicine			
Homeopathy			
Other	(1) Leeches applied weekly for 6 mo., 10/20 patients (non-comparative study).[140] (2) Vitalog (containing 80 mg of Stachytarpheta cayensensis Vahl aqueous dried extract) three times daily for 18 mo., 69/99 lesions (non-comparative study).[141] (3) MEL + khellin + vitamin E > vitamin E*.[38] (4) CO_2 laser + PRP > PRP, 5 mo.[49] (5) PRP > CO_2 laser, 5 mo.[49] (4) Vitilinex + NB-UVB > vitilinex*[73]		
Repigmentation ≥50%			
Ginkgo Biloba			
Pseudocatalase and catalase/dismutase superoxide			
Tetrahydrocurcuminoid cream			
Oral L-phenylalanine			
Chinese herbal medicine			(1) The meta-analysis revealed a statistically significant superior effectiveness in those receiving oral CHM in combination with NB-UVB when compared with phototherapy alone * (five studies: risk difference, 0.22; 95% CI, 0.14-0.29; $p < 0.00001$).[243-247]

Intervention	Our findings	Whitton, M.E. 2015[2]	Chen, Y.J., 2016[7]
Homeopathy	(1) Homeopathy, 190/200 patients, 24 mo. (non-comparative study).[142]		
Other	(1) Leeches applied weekly for 6 mo., 17/20 patients (non-comparative study).[140] (2) Dead sea climatotherapy, 17/436 patients, 4 - 7 wks.[139] (non-comparative study). (3) MEL + khellin + vitamin E > vitamin E*.[38] (3) Vitilinex + NB-UVB > vitilinex*[73]		
Harms			
Ginkgo Biloba			
Pseudocatalase and catalase/dismutase superoxide			
Tetrahydrocurcuminoid cream			
Oral L-phenylalanine			
Chinese herbal medicine			(1) Four of the five RCTs reported side effects including erythema, itching, heart burning, abdominal fullness, and localised itching. But these were mild and without significant renal or liver function impairment.
Homeopathy			
Quality of Life			
Other	OCG + NB-UVB > OCG*, 6 mo.[50]		

Abbreviations: CHM, Chinese herbal medicine; CI, confidence interval; mo., months; NB-UVB, narrow band ultraviolet B; OCG, oral glyrcyrrhizin; PRP, platelet rich plasma; RCTs, randomized controlled trials; UVA, ultraviolet A; wks., weeks.

* indicates a statistically significant result ($p<0.05$)

> denotes the intervention is better than the comparator for the outcome of interest

Comparative studies

Table 9: Included comparative studies investigating topical therapies

Study details	Population	Intervention & Comparator	Outcomes	Comments
Alam, M. N. (2014). JPAD 24: 143-149.[55] RCT, single centre Bangladesh Outpatient 5 mos. f/u	N=60 F: 35; M: 25 **Mean age (SD), yrs.:** group A, 21.50 (3.32); group B, 21.55 (4.12); group C, 22.25 (4.67) **Duration of lesions >1-yr, n (%):** group A, 11 (55%); group B; 6 (30%); group C, 7 (35%) **Duration of lesions < 1-yr, n (%):** group A, 9 (45%); group B, 14 (70%); group C, 13 (65%)	Group A (n=20): betamethasone dipropionate cream (0.05%) in the morning and topical calcipotriene ointment (0.05%) in the evening Group B (n=20): betamethasone dipropionate cream (0.05%) twice daily Group C (n=20): calcipotriene ointment (10%) twice daily Patients were treated daily for 5 mos.	Harms: erythema, scaling, dryness, burning, and pruritus at 1 mo. and five mos.	<u>Continuous outcome with no mean change or SD/SE provided:</u> ○ VASI score of vitiligo in group A, B, and C was 26, 25, and 23, respectively, at baseline; at the final follow up (5 mos.), the respective final score was 3, 8, and 6 ($p<0.05$). N.B. A lower score indicates an improvement in vitiligo.
Alshiyab, D. M., F. A. Al-Qarqaz, et al. (2020). J Dermatolog Treat: 1-4.[56] RCT Jordan Hospital setting 9 mos. f/u	N=49 F: 24; M: 25 **Mean (SD) age, yrs.:** Group A, 10.5 (3.2); Group B, 9.7 (3.6) **Mean duration of vitiligo, yrs.:** Group A, 0.9; Group B, 1.3	Group A (n=25): tacrolimus 0.1% twice daily + topical pseudocatalase/superoxide dismutase gel twice daily Group B (n=24): tacrolimus 0.1% twice daily Patients were treated for 3 mos.	Excellent repigmentation ≥ 75% (>75%) Moderate repigmentation ≥ 50% (>50%)	

Study details	Population	Intervention & Comparator	Outcomes	Comments
Buggiani, G. (2012). Dermatol Ther 25: 472-476.[20] Non-randomized comparative stud, multicentre Czech Republic, Italy, and England Hospital 12 wks. f/u	N=149 F: NR; M: NR **Age range, yrs:** 18-72 **Duration of vitiligo:** NR	Group A (n=37): Re-Pigmenta gel (containing Phenylalanine, Cucumis melo extract and acetyl cysteine) alone Group B (n=43): Bioskin (phototherapy device with a peak emission of NB-UVB at 311nm) alone, once a week Group C (n = 36): Re-pigmenta gel twice daily + Bioskin once a week Group D (n=33): Clobetasol propionate 0.05% twice daily	Repigmentation >50% at 12 wks. Repigmentation ≥75% (>75%) at 12 wks.	<u>Dichotomous outcomes with no/insufficient raw data provided:</u> **Side effects** Mild to moderate side effects (telangiectasias, hypertrichosis, skin atrophy) were observed only in patients treated with clobetasol 0.05% ointment.
Cavalié, M. (2015). J Invest Dermatol 135: 970-974.[21] RCT, bi-centric France: Bordeaux and Nice Hospital 6 mos. f/u	N=35 F: 14; M: 21 **Median (IQR) age, yrs.:** group A, 0.1%, 44.0 (33.0-52.0); group B, 43.0 (38.0-46.5) **Duration of vitiligo, mos.:** NR	Group A (n=19): Tacrolimus (0.1%) ointment twice weekly Group B (n=16): Topical placebo Patients were treated for 6 mos.	QoL: DLQI at 6 mos.	Attrition: Five patients lost to follow up A limitation of this study is the number of patients lost to follow up; four of the five patients that were lost to follow up were in the tacrolimus group, this had a strong impact on the ITT results as the imputation performed was considered a failure in the treatment of all lesions of patients lost to follow-up. PGA Score showed, in the placebo and tacrolimus groups respectively: ○ repigmentation in 11.1% vs. 31% (p = 0.0053); ○ depigmentation in 48.2% vs. 10.4%; ○ no change in 40.7% vs. 58.6% of the lesions

Study details	Population	Intervention & Comparator	Outcomes	Comments
Ebrahim, H. M., R. Elkot, et al. (2020). J Dermatolog Treat: 1-6.[60] RCT Egypt University setting 3 mos. post-treatment f/u	N=48 F: 20; M: 28 **Mean (SD) age, yrs.:** Group A: 36.8 (15.7); Group B: 35.2 (12.9) **Mean (SD) duration of vitiligo, mos.:** Group A, 3.30 (2.45); Group B, 3.16 (2.61)	Group A (n=24): topical tacrolimus 0.1% + microneedling at 2 wk. intervals Group B (n=24): topical tacrolimus 0.1% once daily Treatment for 6 mos.	Repigmentation ≥ 75% (>75%) Repigmentation ≥ 50% Harms: • Itching • Pain	
Ebrahim, H. M. and W. Albalate (2020). J Cosmet Dermatol: 1 - 8[59] RCT, single centre Egypt University 3 mos. post treatment f/u	N=60 F:35; M: 25 **Mean (SD) [range], yrs.:** Group A, 36.52 (8.23) [12 – 60]; Group B, 36.87 (8.56) [13 – 59] **Mean (SD) [range] duration of vitiligo, yrs.:** Group A, 3.24 (1.8) [3-6]; Group B, 3.30 (1.10) [3-7]	Group A (n=30): microneedling intervals + tacrolimus 0.1% at 2 wk. intervals Group B (n=30): tacrolimus 0.1% twice daily Treatment for 6 mos. *N.B. other interventions investigated in this study are presented in table 13*	Repigmentation ≥ 75% Repigmentation ≥ 50% Harms: • Itching • Pain • Erythema	**Attrition:** 0%
Goren, A. (2014). Dermatol Ther 27: 195-197.[22] RCT, single centre Italy	N=15 F: 7; M: 8 **Age:** NR **Duration of vitiligo:** NR	Group A (n=7): Topical cream (Photocil) + natural sunlight exposure, three sessions per wk. Group B (n = 8): Placebo cream + natural sunlight	Repigmentation ≥50% at 3 mos.	**Repigmentation** Of group A, 44% had 30–40% repigmentation. In contrast, only 10% of the patients in group B had 20% repigmentation. The topical cream treatment achieved statistical significance ($p<0.0001$).

Study details	Population	Intervention & Comparator	Outcomes	Comments
Setting, NR 12 wks. f/u		exposure, three sessions per wk. Patients were treated for an average of 11 wks.		
Hu, W., Y. Xu, et al. (2019). Clin Drug Investig 39(12): 1233-1238.[64] RCT, single centre China Hospital setting 6 mos. f/u	N=46 F: 26; M: 18 **Mean (range) age, mos.:** 14.6 (0.2 – 7) **Mean (SD) duration of vitiligo, mos.:** 2.0 (1.5)	Group A (n=23): topical tacrolimus 0.03% Group B (n=23): pimecrolimus 1% Treatment for 6 mos.	Repigmentation ≥75% (>75%) Repigmentation ≥50% (>50%) Harms: mild redness and scratching	Attrition: 0% The median satisfaction scores for the patients' parents were the same for both groups: Group A, 7.0 (2.17) (range 4 – 10); Group B, 7.0 (2.3) (range 3 – 10). A limitation is that the feedback on patient satisfaction was from the parents rather than the infants themselves. The effective rates of vitiligo located on the head and neck (70%), trunk (64.3%), and perineum (100%) were higher than the effective rates of the extremities (50%), p<0.05
Iraji, F. (2017). AdvBiomedRese 6: 34.[46] RCT Tehran Hospital setting 12 wks. f/u	N=88 F: 45; M: 43 **Mean age (SD), yrs.:** group A, 36.5(10.2); group B, 35.7(10.5)	Group A (n=44): betamethasone valerate 0.1% cream + oral simvastatin 40mg, twice daily Group B (n=44): betamethasone valerate 0.1% cream, twice daily Patients were treated for 12 wks.	Repigmentation ≥50% (>50%) at 12 wks.	At the end of the study 42 participants failed to complete the study. Thirty-nine subjects (16 subjects in Group A and 23 subjects in Group B) excluded from the study due to persistence of lesions after 8th week of treatment or aggravation of lesions and 3 subjects (1 subject in Group A and 2 subjects in Group B) gave up the study due to scheduling difficulties.
Mohamed, H. A. (2015). J Cosmet	N=68 F: NR; M: NR	Group A (n=955): CO_2 laser plus 5-FU topical cream once	Repigmentation ≥75% at 6 mos.	Attrition: 4 patients lost to follow up.

Study details	Population	Intervention & Comparator	Outcomes	Comments
Laser Ther 17: 216-223.[23] RCT, single-blind, single centre Egypt Outpatient unit 6 mos. f/u	**Mean age (SD), yrs.**: group A, 37.9 (17.7); group B, 38.4 (10.1); group C, 40.6 (11.3) **Mean duration of vitiligo (SD), yrs.: g**roup A, 8 (1.1); group B, 9.7(0.4); group C, 9 (1.3)	daily for 7 days, successive sessions were repeated monthly. Group B (n=703): 5-FU topical cream, once daily for 7 days/mo. Group C (n=601): CO_2 laser monthly. Patients were treated for 5 mos. *N.B. other interventions investigated in this study are presented in table 11.*	Repigmentation ≥50% at 6 mos.	<u>Dichotomous outcomes with no/insufficient raw data provided:</u> **Side effects:** ○ Patients across group A and C experienced more frequent side effects as compared with the patients in group B. But this difference was not statistically significant except for transient hyperpigmentation. ○ Across group A and C, infection was detected in 19% of patients, itching was noted in 19% of patients, and transient hyperpigmentation was detected in all patients. The hyperpigmentation was accepted by patients more than the vitiligous skin colour and these areas returned to normal skin colour within a few wks. to mos.
Rafiq, Z. (2016). JPAD 26: 123-128.[47] RCT Pakistan Hospital setting 6 mos. f/u	N=60 F: 30; M: 30 **Mean age (SD), yrs.:** group A, 22.27 (9.22); group B, 24.97 (11.2) **Duration of vitiligo:** < 2 yrs	Group A (n=30): tacrolimus 0.03% Group B (n=30): clobetasol 0.05%	Repigmentation ≥75% (>75%) at 6 mos. Repigmentation ≥50% (>50%) at 6 mos.	

Study details	Population	Intervention & Comparator	Outcomes	Comments
Shah, B., K. Godse, et al. (2019). Dermatol Ther 32(6): e13109.[70] Open-label RCT (multicentre) India Hospital setting 12 mos. f/u	N=84 (94 randomized) F: 37; M: 47 **Mean (SD) age, yrs.:** Group A, 38.3 (13.23); Group B, 37.91 (12.55)	Group A (n=40): bFGF related decapeptide solution + tacrolimus 0.1% Group B (n=44): topical tacrolimus 0.1% Treatment for 12 mos.	Repigmentation ≥50% (>50%)	Attrition: 10.6% (lost to follow-up) Minimal adverse effects were reported. An interim analysis so complete data is not available for analysis
Shehzad, A. (2007). JPAD 17: 89-94.[54] RCT, single centre India Hospital setting 6 mos. f/u	N=60 F: 34; M: 26 **Mean age (SD), yrs.:** group A, 21.2 (10.8); group B, 25.3 (11.9) **Mean duration of vitiligo (SD), yrs.:** Group A, 1.7 (1.5); Group B, 1.8 (1.4).	Group A (n=30): calcipotriol + PUVA, thrice weekly Group B (n = 30): calcipotriol, twice daily Patients were treated for 6 mos.	Repigmentation ≥75% (>75%) at 6 mos. Harms: erythema, pruritus and nausea at 6 mos.	Patients were only included if they showed no evidence of spontaneous repigmentation, the duration of their disease was <5 years and they had received no treatment for the last 2 mos.
Thomas, K.S. (2020) Br J Dermatol n/a : n/a[76] Multi-centre (16 UK hospitals) RCT UK	N=517 F: 249; M: 268 **Mean (SD) age of adults (n = 398):** Group A, 37.0 (19.1); Group B, 38.6 (20.0); Group C, 36.9 (18.9) **Mean (SD) age of children (n = 119):** Group A, 10.6 (3.3); Group B, 11.7 (3.7); Group C, 10.8 (3.5)	Group A (n=175): topical corticosteroid (mometasone furoate 0.1%) + hand-held NB-UVB on alternate days, dose escalation dependent on erythema Group B (n=173): topical corticosteroid (mometasone furoate 0.1%) once daily on alternative wks. + dummy	Repigmentation ≥75% at 9 mos. Participant-reported treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9 mos. Harms: • Treatment-related adverse events • Erythema	Attrition at 9 mos.: 147/517 (28.4%); not assessed in clinic (n=4), withdrew consent (n = 60), discontinued due to AE (n=3), lost to follow-up (n=75), other reasons (n=5). Attrition at 21 mos. f/u: 293/517 (56.7%)

Study details	Population	Intervention & Comparator	Outcomes	Comments
Home based 21 mos. f/u	**Median duration of vitiligo, yrs.:** Group A, 7; Group B, 7; Group C, 5 **Inclusion criteria:** people with vitiligo (including those with lighter skin types); adults and children **Exclusion criteria:** Widespread vitiligo	hand-held NB-UVB on alternate days Treatment for 9 mos. *N.B. Other interventions investigated in this study are presented in table 11*	• Skin thinning QoL*: • VitiQoL, Skindex 29 in adults at 21 mos. • EQ5D utility at 9 mos. • CHU9D in children at 9 mos. Maintenance of treatment success at 21 mos.	
Zaib (2017). Pak J MedHealth Sci 11: 616-619.[48] RCT Pakistan Hospital setting 3 mos. f/u	N=66 F: 38; M: 28 **Mean age (SD), yrs.:** group A, 26.1(7.2)**;** group B, 26.4(8.7)	Group A (n=33): 0.03% tacrolimus ointment, twice daily Group B (n=33): 0.1% betamethasone valerate, twice daily Patients were treated for 3 mos.	≥50% repigmentation at 3-mo. follow-up.	Data for 1-mo. and 2-mo. follow-up was reported, but only long-term (3-mo.) data was extracted.

Abbreviations: 5-FU, 5-fluorouracil; BSA, body surface area; bFGF, basic Fibroblast Growth Factor; DLQI, dermatology life quality index; F, female; FP, fluticasone propionate; FAD, food and drug administration; IQR, interquartile range; ITT, intention to treat; NB-UVB, narrow band-ultraviolet B; M, male; NR, not reported; PGA, physician global assessment; PUVAsol, psoralen ultraviolet A; PC-KUS, pseudocatalase; RCT, randomized controlled trial; SD, standard deviation; VAS, visual analogue score; wks., wks.; yrs., years.
* Lower score indicates an improvement in VitiQOL, Skindex and CHU9D; higher score indicates an improvement in EQ5D.

Table 10: Included comparative studies investigating systemic therapies

Study details	Population	Intervention	Outcomes	Comments
Singh, A. (2014). Indian J Dermatol Venereol Leprol 80: 29-35.[24]	N=50 F: 20; M: 30 **Mean age (SD), yrs.**: group A, 35.20 (14.10); group B, 25.96 (12.53)	Group A (n=25): minocycline 100 mg/day	Repigmentation ≥75% (>75%) at 6 mos. Harms: adverse effects at 6 mos.	The authors noted that a limitation of the study was a lack of a placebo group but highlighted that when compared with historical placebo groups, both OMP and minocycline group showed

Study details	Population	Intervention	Outcomes	Comments
RCT, single centre Clinic India 6 mos. f/u	**Mean duration of vitiligo (SD), mos.:** group A, 63.84 (63.75); group B, 36.96 (32.11)	Group B (n=25): OMP corticosteroid therapy (2.5 mg of dexamethasone on two consecutive days in a week) Patients were treated for 6 mos.	Cessation of spreading of vitiligo: number of patients without any new lesions at 6 mos.	highly significant better efficacy compared with placebo (p<0.001).
Singh, H. (2015). Dermatology 231: 286-290[25] RCT, open label, single centre Clinic India 6 mos. f/u	N=52 F: 24; M: 28 **Mean age (SD):** group A, 38.60 (12.52); group B, 32.68 (15.48) **Mean (SD) duration of vitiligo, mos.:** group A, 124.76 (125.18); group B, 67.02 (87.71)	Group A (n=26): low dose (10 mg) oral MTX per week, and folic acid 2.5 mg a day prior to and on the day after MTX. Group B (n=26): Corticosteroid OMP which comprised of five 2.5 mg dexamethasone tablets taken on 2 consecutive days a wk. Patients were treated for 6 mos.	Harms: adverse effects at 6 mos.	Attrition: one patient in group A discontinued MTX because of severe nausea, and one patient in the OMP group was lost to follow up. So, 50 patients completed the study.

Abbreviations: CBC, complete blood count; CDLQI, children's dermatology life quality index; F, female; ITT, intention to treat; M, male; MTX, methotrexate; OCG, oral compound glycyrrhizin; OMP, oral minipulses; RCT, randomized controlled trial; SD, standard deviation; VIDA, vitiligo disease activity score; vitiligo disease VASI, vitiligo area scoring index; VETF, Vitiligo European Task Force; yrs., years.

Table 11: Included comparative studies investigating light and laser therapies

Study details	Population	Intervention & Comparator	Outcomes	Comments
Abdelghani, R. (2017). J Cosmet Dermatol.[49] RCT, single centre Egypt University setting 5 mos. f/u	N=80 F: 50; M: 30 **Mean age (SD), yrs.:** group A, 36.95 (13.04); group B, 29.60 (10.80) **Mean vitiligo duration:** <2 years, 34; >2 years, 46	Group A (n=20): CO_2 laser + NB-UVB, same as protocol A for CO_2 laser; 1 week after each laser session, patients received two NB-UVB phototherapy sessions per wk. Group B (n=20): CO_2 laser, 4 sessions with 2-wk interval Patients were treated for 2 mos.	Repigmentation ≥75% (>75%) at 5 mos.	Harms: erythema, itching, burning sensation, ecchymosis

Study details	Population	Intervention & Comparator	Outcomes	Comments
		N.B. Other interventions investigated by this study are presented in table 12 and 15.		
Bhatnagar, A. (2007). J Eur Acad Dermatol Venereol 21: 1381-1385.[26] RCT, single centre India Clinic 6 mos. f/u	N=50 F: 32; M: 18 **Mean age (SD), yrs.:** group A, 28.96 (10.64); group B, 26.64 (11.13) **Mean duration of vitiligo (SD), yrs.:** group A, 11.24 (7.6); group B, 4.36 (2.94)	Group A (n=25): NB-UVB thrice weekly on non-consecutive days Group B (n=25): PUVA thrice weekly on non-consecutive days Patients were treated for an average of 6 mos.	Repigmentation ≥50% (> 50%) at 6 mos.	The activity of vitiligo before the start of NB-UVB did not influence results of repigmentation. However, patients with active disease had statistically less pigmentation in the PUVA group. Therefore, PUVA seems to be less effective in unstable disease.
Eleftheriadou, V. (2014). Trials 15: 51.[27] RCT, double blind multicentre UK Hospital 4 mos. f/u	N=29 F: 15; M: 14 **Mean age (SD), yrs.:** 31.7 ± 17.9 **Mean duration of vitiligo (SD), yrs.:** 12.28 (9.67)	Group A (n=19): Home intervention of light therapy (hand-held NB-UVB phototherapy). Within the active groups, patients were randomized to the Dermfix or Waldmann device. Group B (n=10): Placebo device (identical to the Dermfix 1000 device, with the only difference being a plastic cover blocking the emission of the NB-UVB rays). Patients were treated for 4 mos.	Repigmentation ≥75% at 4 mos. Harms: erythema, pruritus, hyperpigmentation around the lesions, dry skin, cold sores QoL: DLQI at 4 mos. Cessation of spreading of vitiligo at 4 mos.	Attrition: three patients withdrew from the treatment and only one patient was lost to follow up. Dichotomous outcomes with insufficient raw data: **Side effects:** ○ In group A, pruritus (7% (2/29)), hyperpigmentation around the lesions (10% (3/29)) and dry skin (10% (3/29)), cold sores (3% (1/29)). ○ Except for erythema, no other side effects were reported in group B.

Study details	Population	Intervention & Comparator	Outcomes	Comments
Elgoweini, M. (2009). J Clin Pharmacol 49: 852-855.[28] RCT, single centre Egypt Dermatology department of a university 6 mos. f/u	N=24 F: 14; M: 10 **Age range, yrs.:** group A, 20-50; group B, 19-48 **Mean duration of vitiligo (SD), yrs.:** 3.3 (2.1)	Group A (n=12): NB-UVB (thrice weekly on non-consecutive days) plus oral vitamin E (once daily started 2 wks before NB-UVB). Group B (n=12): NB-UVB thrice weekly on non-consecutive days. Patients were treated for 6 mos.	Harms: erythema at 6 mos. Repigmentation ≥50% (>50%) at 6 mos.	Attrition: four patients discontinued due to reasons unrelated to the treatment.
Elshafy Khashaba, S. A. (2018). Journal of the American Academy of Dermatology 79: 365-367. [62] RCT Egypt University setting 3 mos. f/u	N=40 F: 22; M: 18 **Mean (SD) age, yrs.:** Group A, 25.30 (8.55); Group B, 24.10 (6.65) **Mean (SD) duration of vitiligo, mos.:** Group A, 14.70 (9.50); Group B, 16.05 (9.73)	Group A (n=20): micro-needling + triamcinolone solution (10 mg /mL) + NB-UVB Group B (n=20): NB-UVB Treatment for 3 mos. *N.B. other interventions investigated in this study are presented in table 12 and 13*	Repigmentation ≥ 75% (>75%) Repigmentation ≥ 50% (>50 %)	The overall incidence of side effects were minimal, except for pain.

Study details	Population	Intervention & Comparator	Outcomes	Comments
Khattab, F. M., E. Abdelbary, et al. (2019). J Cosmet Dermatol 19 (4): 869 – 877[65] RCT, single centre Egypt Outpatient 3 mos. post-treatment f/u	N=52 F: 42; M: 10 **Mean (SD) age, yrs.:** Group A, 25.42 (7.60); Group B, 24.90 (5.60)	Group A (n=26): intradermal PRP injection every 3 wks. + excimer laser two times a wk. Group B (n=26): excimer laser two times a wk. Treatment for 4 mos.	Repigmentation ≥ 75% Repigmentation ≥ 50%	**Side effects:** • Pain in 6 (23%) of patients in group A, mild and tolerable Symptomatic erythema in 4 (15.4%) of patients in group B
Khemis, A., E. Fontas, et al. (2020). J Invest Dermatol.[66] RCT, single centre France Hospital 24 wks. f/u	N=80 F: 49; M: 28 **Mean (SD) age, yrs.:** Group A, 45.4 (13.2); Group B, 49.5 (13.4) **Mean (SD) duration of vitiligo, yrs.:** Group A, 18.6 (13.8); Group B, 22.7 (15.0)	Group A (n=40): Apremilast + NB-UVB Group B (n=40): placebo + NB-UVB Treatment for 24 wks.	DLQI	**Attrition:** total, 5/80, 6%; Group A, 2/40 lost to follow up and 1/40 refused to continue; Group B, 2/40 lost to follow-up and 1/40 withdrew consent.

Study details	Population	Intervention & Comparator	Outcomes	Comments
Li, L. (2019). Pediatric Dermatology 36: e53-e55.[68] RCT, single centre China Hospital 12 wks. f/u	N=233 F: NR; M: NR **Mean (SD) age, yrs.:** NR (paediatric patients) **Duration of vitiligo:** NR	Group A (77 lesions): tacrolimus 0.1% twice daily + excimer laser twice weekly Group B (74 lesions): pimecrolimus 1% twice daily + excimer laser Group C (82 lesions): halometasone twice daily + excimer laser Group D (78 lesions): excimer laser Treatment for 12 wks. *N.B. other interventions investigated in this study are presented in table 12*	Complete repigmentation Repigmentation ≥ 50% (>50%)	**Attrition:** 69/233 (30%)
Li, L. (2019). Australasian Journal of Dermatology 60: e85-e86[67] RCT, single centre China Hospital 12 wks. f/u	N=152 F: 74; M: 78 **Mean (SD) age, yrs.:** Group A, 47 (5.5); Group B, 46 (6.1); Group C, 51 (4.9)	Group A (57 lesions): excimer laser twice weekly + tacrolimus 0.1% once daily Group B (71 lesions): excimer laser twice weekly + halometasone twice daily Group C (53 lesions): excimer laser Treatment for 12 wks. *N.B. other interventions investigated by this study are presented in table 12*	Complete repigmentation Repigmentation ≥ 50% (>50%)	
Lim, H. W. (2015). JAMA Dermatol 151: 42-50.[29]	N=55 F: 34; M: 21	Group A (n = 28): Afamelanotide implant (four times a mo.) plus NB-UVB	Harms: adverse events at 6 mos.	Attrition: one patient from each group failed to receive at least one treatment.

Study details	Population	Intervention & Comparator	Outcomes	Comments
RCT, multicentre USA Outpatient 6 mos. f/u	**Mean age (SD) [range], yrs.:** group A, 46.5 (16.3) [18-79]; group B, 46.1 (12.5) [23-67] **Mean duration of vitiligo (SD) [range], yrs.**: group A, 5.4 (5.5) [1-26]; group B, 6.3 (6.2) [1-29]	phototherapy twice/thrice weekly for 6 mos. Group B (n = 27): NB-UVB phototherapy twice/thrice weekly for 6 mos. followed by a 6 mos. observation period.		Continuous outcome with no mean change or SD/SE provided: **Response to treatment evaluated by the VASI in the ITT population:** ○ In both groups, the degree of repigmentation improved ($p < 0.001$), as reflected by the decreased VASI observed from day 56 until the end of the observation period (day 168). ○ Between group comparison showed that response in group A was superior to that in the group B ($p<0.05$). ○ Repigmentation (represented by relative reduction in the VASI), Group A 48.64% (95% CI, 39.49% - 57.80%) vs. Group B 33.26% (95% CI, 24.18%-42.33%) at day 168.
Liu, B., Y. Sun, et al. (2020). Photodermatol Photoimmunol Photomed 36(1): 14-20.[69] RCT China Hospital	N=100 (122 randomized) F: 58; M: 42 **Mean (SD) age, yrs.:** Group A, 25.44 (1.432); Group B, 27.44 (1.358)	Group A (n=61): Home-based NB-UVB treatment thrice a week Group B (n=61): Hospital-based NB-UVB treatment thrice a week Treatment for 3 mos.	Repigmentation ≥ 75% Repigmentation ≥ 50% QoL (VitiQoL scores)	**Attrition:** Group A, 9/61 (rapid progression of vitiligo, n = 3; segmental vitiligo diagnosis, n = 4; personal reasons, n = 2); Group B, 13/61 (rapid progression of vitiligo, n = 2; segmental vitiligo diagnosis, n =2; missed more than 10 treatments, n = 8; personal reasons, n =1) **Adverse events:** Group A: no serious adverse events Group B: mild burning (n = 6); painful erythema and burning sensation (n =

Study details	Population	Intervention & Comparator	Outcomes	Comments
3 mos. f/u for repigmentation 20-wk. f/u for QoL				16); blistering (n=2); Koebner phenomenon and enlarged vitiligo patch (n=1); excessive hyperpigmentation (n=10)
Lotti, T. (2008). Dermatol Ther 21 Suppl 1: S20-26.[30] Non-randomized comparative study, multicentre Italy, Czech Republic, and Belgium University setting 6 mos. f/u	n=470 F: 261; M: 209 **Age range, yrs.:** 18-72 **Vitiligo duration (yrs.), n:** <1, 65 1-5, 118 6-10, 134 11-20, 83 21-30, 34 31-40, 29 >40, 7	Group A (n=100): Bioskin alone Group B: 0.1% tacrolimus + Bioskin (59) Group C (n=63): 1% pimecrolimus + Bioskin Group D (n=28): betamethasone dipropionate 0.05% + Bioskin Group E (n=60): calcipotriol ointment 50 µg/g + Bioskin Group F (n=60): 10% L-phenylalanine + Bioskin Group G (n=22): 0.1% tacrolimus alone Group H (n=19): 1% pimecrolimus alone Group I (n=23): betamethasone dipropionate 0.05% alone Group J (n=18): calcipotriol ointment 50 µg/g Group K (n=18): 10% L-phenylalanine alone Patients were treated for 6 mos.	Repigmentation ≥50% (> 50%) at 6 mos. Repigmentation ≥75% (>75%) at 6 mos.	Attrition: 12 patients stopped therapy due to personal reasons.

Study details	Population	Intervention & Comparator	Outcomes	Comments
Mohamed, H. A. (2015). J Cosmet Laser Ther 17: 216-223.[23] RCT, single-blind, single centre Egypt Outpatient 6 mos. f/u	N=68 F: NR; M: NR **Mean age (SD), yrs.**: group A, 37.9 (17.7); group B, 38.4 (10.1); group C, 40.6 (11.3) **Mean duration of vitiligo (SD), yrs.:** group A, 8 (1.1); group B, 9.7(0.4); group C, 9 (1.3)	Group A (n=955): CO_2 laser plus 5-FU topical cream OD, for 7 days/mo. Group B (n=703): 5-FU topical cream, OD for 7 days/mo. Group C (n=601): CO_2 laser monthly Patients were treated for 5 mos. *N.B. other interventions investigated by this study are presented in table 9.*	Repigmentation ≥75% at 6 mos. Repigmentation 100% at 6 mos. Repigmentation ≥50% at 6 mos.	Attrition: 4 patients lost to follow up. Dichotomous outcomes with no/insufficient raw data provided: **Side effects** ○ Patients across group A and C experienced more frequent side effects compared with the patients in group B. But this difference was not statistically significant except for transient hyperpigmentation. Across group A and C, infection was detected in 19% of patients, itching was noted in 19% of patients, and transient hyperpigmentation was detected in all patients. The hyperpigmentation was accepted by patients more than the vitiligous skin colour and these areas returned to normal skin colour within a few wks. to mos.
Mou, K. H. (2016). Braz J Med Biol Res 49.[50] Open-label RCT, single-centre Hospital China 6 mos. f/u	N=144 F: NR; M: NR **Age (range), yrs.:** 3 – 48	Group A (n=48): OCG + UVB (dosage as for group A and group B) Group B (n=48): UVB, twice weekly Patients were followed-up for 6 mos. *N.B. Other interventions investigated by this study are presented in table 15.*	QoL: DLQ at 6 mos.	**Effectiveness rate:** • 87.5% repigmentation rate in group A (42/48) • 75.0% repigmentation rate in group B (36/48) The differences in effectiveness rate between group A and B were significant ($p < 0.05$).

Study details	Population	Intervention & Comparator	Outcomes	Comments
				VIDA score: Score decreased in all groups during treatment, showing both OCG and UVB to be effective. In the 2nd and 6th mos. of treatment, group A scores were significantly lower than group B ($p < 0.05$).
Nistico, S. (2015). Global Dermatol 2: 93-96.[37] Non-randomized single centre comparative cohort study Italy University setting 3 mos. f/u	N=32 F: 16; M: 16 **Mean age, yrs. (range):** 41.2 (10-72) **Mean duration of vitiligo (range), yrs.:** 9 (1-45)	Group A (n=4): MEL associated with topical khellin 4% and topical tacrolimus 0.1% Group B (n=4): MEL associated with topical tacrolimus 0.1% Group C (n=4): MEL associated with topical khellin 4% Group D (n=4): MEL (control group) Patients were treated for 3 mos. *N.B. Other interventions investigated by this study are presented in table 12.*	Repigmentation ≥75% (>75%) at 3 mos. Complete repigmentation (100%) at 3 mos. Repigmentation ≥50% (>50%) at 3 mos. Harms: Erythema, burning-pain, perilesional hyperpigmentation at 3 mos.	**Repigmentation:** ○ Poor-moderate repigmentation (1-50%): Group C, 2/8 patients Group D, 4/8 patients ○ Moderate repigmentation (26%-50%): Group A, 4/8 patients Group B, 3/8 patients
Singh, S. (2013). J Eur Acad Dermatol Venereol 27: 1344-1351.[31] Non-randomized comparative study, single centre India	N=35 F: 15; M: 20 **Mean age (range), yrs:** Group A, 27.33 (16-41); Group B, 31.76 (12-49) **Mean duration of vitiligo (range), yrs:** Group A, 8.94 (1-20); Group B, 10.37 (0.33-20)	Group A (n=18): Oral PUVA Group B (n=17): PUVA sol Patients were treated for 36 wks. Both treatments were given on alternate days.	Repigmentation ≥75% (>75%) at 36 wks. Repigmentation ≥50% (>50%) at 36 wks.	Attrition: in total 16 patients were lost to follow-up, six patients from group A and 10 patients from group B. **Mean (SD) QoL at 36 wks.:** PUVA, 10.5 (7.6); PUVA sol, 3.6 (2.8) $p = 0.04$ (A higher score represents better QoL)

Study details	Population	Intervention & Comparator	Outcomes	Comments
Outpatient 36 wks. f/u				
Tien Guan, S. T. (2015). J Am Acad Dermatol 72: 733-735.[32] RCT, single centre Clinic Singapore 6 mos. f/u	N=44 F: 16; M: 28 **Median age (range), yrs.:** group A, 23.5 (15-40); group B, 26.5 (5-66) **Median duration (range) of disease, yrs.:** group A, 2(1-16); group B, 3(0.5-10)	Group A (n=22): Home based phototherapy thrice weekly Group B (n=22): Institution-based excimer lamp treatment twice a wk. Patients were treated for 6 mos.	Repigmentation ≥75% (>75%) at 6 mos. Repigmentation ≥50% (>50%) at 6 mos.	In terms of side effects, there was only one case of phototherapy burn caused by overenthusiastic (excessive) application in group A but subsequently the patient recovered.
Thomas, K.S. (2020) Br J Dermatol n/a : n/a[76] Multi-centre (16 UK hospitals) RCT UK Hospital setting 21 mos. f/u	N=517 F: 249; M: 268 **Mean (SD) age of adults (n = 398):** Group A, 37.0 (19.1); Group B, 38.6 (20.0); Group C, 36.9 (18.9) **Mean (SD) age of children (n =119):** Group A, 10.6 (3.3); Group B, 11.7 (3.7); Group C, 10.8 (3.5) **Median duration of vitiligo, yrs.:** Group A, 7; Group B, 7; Group C, 5 **Inclusion criteria:** people with vitiligo (including those with lighter skin types); adults and children **Exclusion criteria:**	Group A (n=175): topical corticosteroid (mometasone furoate 0.1%) + hand-held NB-UVB on alternate days, dose escalation dependent on erythema Group B (n=169): hand-held NB-UVB on alternate days, dose escalation dependent on erythema + placebo ointment Treatment for 9 mos. *N.B. Other interventions investigated by this study are presented in table 9*	Repigmentation ≥75% at 9 mos. Participant-reported treatment success (a lot less noticeable or no longer noticeable) on VNS scale at 9 mos. Harms: • Treatment-related adverse events • Erythema • Skin thinning QoL*: • VitiQoL, Skindex 29 in adults at 21 mos. • EQ5D utility at 9 mos.	Attrition at 9 mos.: 147/517 (28.4%); not assessed in clinic (n=4), withdrew consent (n=60), discontinued due to AE (n=3), lost to follow-up (n=75), other reasons (n = 5). Attrition at 21 mos. f/u: 293/517 (56.7%)

Study details	Population	Intervention & Comparator	Outcomes	Comments
	Widespread vitiligo		• CHU9D in children at 9 mos. Maintenance of treatment success at 21 mos.	
Van, T. N. (2019). Open access Macedonian journal of medical sciences 7: 283-286.[73] RCT Italy Hospital 12 wks. f/u	N=62 F: 36; M: 26 **Mean (range) age, yrs.:** 34.5 (18 – 58) **Duration of vitiligo:** NR	Group A (n=35): Vitilinex + NB-UVB 311 nm Group B (n=16): NB-UVB 311 nm Treatment for 12 wks. *N.B. other interventions investigated in this study are presented in table 15*	Repigmentation ≥ 75% (>75%) Repigmentation ≥ 50% (>50%)	
Yuksel, E. P. (2009). Eur J Dermatol 19: 341-344.[34] Non-randomized comparative study, single centre Hospital Turkey 6 mos. f/u	N=30 F: 18; M: 12 **Mean (SD) age, yrs:** 34 (13) **Median duration of vitiligo (range), yrs.:** group A, 3(1-28); group B, 10(2-20)	Group A (n=21 lesions): NB-UVB + catalase-superoxide (Vitix gel) Group B (n=21 lesions): NB-UVB 21 lesions from each group were evaluated. Patients were treated for 6 mos.	Repigmentation ≥75% (>75%) at 6 mos. Repigmentation ≥50% (>50%) at 6 mos.	

Study details	Population	Intervention & Comparator	Outcomes	Comments
Zhang, C. (2017). J Dermatolog Treat 28: 668-671.[53] Randomized comparative study, single centre study Hospital China 6 mos. f/u	N=233 F: 142; M:91 **Mean age (SD), yrs.:** group A, 30.2 (5.4); group B, 31.5(6.3); group C, 27.8 (5.1)	Group A (n=80): Yiqiqubai granule 20g twice daily + 308nm laser once a week Group B (n=78): 308-nm excimer laser once a week Group C (n=75): Yiqiqubai granule 20g twice daily Patients were treated for 6 mos. *N.B. Other interventions investigated by this study are presented in Table 14*	Repigmentation ≥ 50% at 6 mos. Change in QoL at 6-mos. for: embarrassment, dress, social, and work.	
Zhang, L. (2019). Photodermatology, photoimmunology & photomedicine.[74] Prospective cohort China Outpatient 6 mos. f/u	N=94 F: 48; M: 46 **Mean (SD) age, yrs.:** Group A, 33.0 (12.2); Group B, 37.7 (15.3) **Mean (SD) duration, yrs.:** Group A, 5.3 (7.4); Group B, 7.3 (7.0)	Group A (n=48): Home-based NB-UVB treatment thrice weekly on non-consecutive days Group B (n=46): Outpatient NB-UVB twice weekly on non-consecutive days Treatment for 6 mos.	Repigmentation ≥ 75% Repigmentation ≥ 50% QoL (vitiQoL) **Harms:** Painful erythema Pruritus Skin burning sensation	

Abbreviations: 5-FU, fluorouracil; CI, confidence interval; CO_2, carbon dioxide; DLQI, Dermatology Quality of Life Index; F, female; ITT, intention to treat; M, male; NB-UVB, narrow band ultraviolet B; NR, not reported; OCG, oral compound glycyrrhizin; PUVA, psoralen ultraviolet A; QoL, quality of life; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SPT, skin phototype; VASI, vitiligo area scoring index; VitiQoL, Vitiligo Quality of Life index; wks., weeks; yrs., years.

Table 12: Included comparative studies investigating combination therapies

Study details	Population	Intervention & Comparator	Outcomes	Comments
Abdelghani, R. (2017). JCosmetDermatol.[49] RCT, single centre Egypt University setting 5 mos. f/u	N=80 F: 50; M: 30 **Mean age (SD), yrs.:** group A, 33.90 (11.89); group B, 36.95 (13.04) **Mean disease duration:** <2 years, 34; >2 years, 46	Group A (n=20): CO_2 laser + PRP, same as protocol for group A and B Group B (n=20): CO_2 laser + NB-UVB, same as protocol A for CO_2 laser; 1 week after each laser session, patients received two NB-UVB phototherapy sessions per week. Patients were treated for 2 mos. *N.B. Other interventions investigated by this study are presented in table 11 and 15.*	Repigmentation ≥75% (>75%) at 5 mos.	Harms: erythema, itching, burning sensation, ecchymosis
Barman, K. D. (2004). Dermatol Surg 30: 49-53.[35] RCT, single centre India Outpatient 6 mos. f/u	N=50 F: 27; M: 23 **Mean age, yrs.:** 22.52 **Mean duration of vitiligo (range), yrs.:** 7.33 (1.5-26)	Group A (n=22): Punch grafting followed by PUVA, twice a wk. Group B (n=28): Punch grafting followed by topical fluocinolone acetonide (0.1%), once daily. PUVA or topical fluocinolone acetonide (0.1%) were started after 4 wks. of grafting. Patients were treated for 6 mos.	Cosmetic acceptability of the colour match at 6 mos.	Attrition: six patients lost to follow up
Elshafy Khashaba, S. A. (2018). Journal of the American Academy of Dermatology 79: 365-367.[62]	N=40 F: 25; M: 15 **Mean age (SD), yrs.:** group A, 25.30 (8.55); group B, 28.05 (10.12)	Group A (n= 20): NB-UVB + micro-needling + topical triamcinolone solution (10mg/mL), once weekly	Repigmentation ≥75% (>75%) at 3 mos. Repigmentation ≥50% (>50%) at 3 mos.	

Study details	Population	Intervention & Comparator	Outcomes	Comments
RCT, single centre Egypt University setting 3 mos. f/u	**Mean disease duration (SD), mos.:** group A, 14.70 (9.50); group B, 20.30 (14.50)	Group B (n=20): micro-needling + topical triamcinolone solution (10mg/mL), once weekly *N.B. Other interventions investigated by this study are presented in table 11 and 13*		
Li, L. (2016). J Cosmet Laser Ther 18: 182-185.[36] RCT, single centre China Hospital 6 mos. f/u	N=50 F: 25; M: 14 **Mean age (range), yrs.:** 35 (18-53) **Duration of vitiligo, mos.:** NR	Group A (n=26): Alpha-lipoic acid once daily + betamethasone injection (three times at one-mo. intervals) + NB-UVB phototherapy (every 2-3 mos.) Group B (n=24): Placebo once daily + betamethasone injection (three times at one-mo. intervals) + NB-UVB phototherapy (every 2-3 mos.) Patients were treated for 6 mos.	Repigmentation ≥75% (>75%) at 3 mos. and 6 mos. Repigmentation ≥50% (>50%) at 3 mos. and 6 mos.	Attrition: A total of 50 patients were enrolled, however only 39 of them completed the therapy. <u>Dichotomous outcomes with no/insufficient raw data provided:</u> **Side effects:** ○ Nine patients reported nausea or dizziness after orally taking alpha-lipoic acid (time point not specified). The symptoms disappeared by stopping the intake of alpha-lipoic acid for several days or changing the time of its intake. ○ NB-UVB related side effects included mild erythema, slight oedema, blistering,

Study details	Population	Intervention & Comparator	Outcomes	Comments
				roughness, mild-to-moderate itching, and burning sensation. ○ Seven patients reported weight gain after betamethasone injection, but their weights were reduced to baseline after 1-3 mos.
Li, L. (2019). Australasian Journal of Dermatology 60; e85-e86[67] RCT, single centre China Hospital 12 wks. f/u	N=152 F: 74; M: 78 **Mean (SD) age, yrs.:** Group A, 47 (5.5); Group B, 46 (6.1); Group C, 51 (4.9)	Group A (n=51): excimer laser twice weekly + tacrolimus 0.1% once daily Group B (n=53): excimer laser twice weekly + halometasone twice daily Treatment for 12 wks. *N.B. other interventions investigated in this study are presented in table 11*	Complete repigmentation Repigmentation ≥ 50% (> 50%)	
Li, L. (2019). Pediatric Dermatology 36: e53-e55.[68] RCT, single centre China Hospital 12 wks. f/u	N=233 F: NR; M: NR **Mean (SD) age, yrs.:** NR (paediatric patients) **Duration of vitiligo:** NR	Group A (n=77): tacrolimus 0.1% twice daily + excimer laser twice weekly Group B (n=74): pimecrolimus 1% twice daily + excimer laser Group C (n=82): halometasone twice daily + excimer laser One lesion was treated in each participant. Treatment for 12 wks.	Repigmentation ≥ 50% (> 50%) Complete repigmentation	**Attrition:** 69/233 (30%)

Study details	Population	Intervention & Comparator	Outcomes	Comments
		N.B. other interventions investigated in this study are presented in table 11		
Nistico, S. (2015). Global Dermatol 2: 93-96.[37] Non-randomized single centre comparative cohort study Italy University setting 3 mos. f/u	N=32 F: 16; M: 16 **Mean age, yrs. (range):** 41.2 (10-72) **Mean duration of vitiligo (range), yrs.:** 9 (1-45)	Group A (n=8): MEL associated with topical khellin 4% and topical tacrolimus 0.1% Group B (n=8): MEL associated with topical tacrolimus 0.1% Group C (n=8): MEL associated with topical khellin 4% Group D (n=8): MEL (control group) Patients were treated for 3 mos. *N.B. other interventions investigated by this study are presented in table 11.*	Repigmentation ≥75% (>75%) at 3 mos. Complete repigmentation (100%) at 3 mos. Repigmentation ≥50% (>50%) at 3 mos. Harms: Erythema, burning-pain, perilesional hyperpigmentation at 3 mos.	**Repigmentation:** ○ Poor-moderate repigmentation (1-50%): Group C, 2/8 patients Group D, 4/8 patients ○ Moderate repigmentation (26%-50%): Group A, 4/8 patients Group B, 3/8 patients
Saraceno, R. (2009). Dermatol Ther 22: 391-394.[38] Non-randomized comparative study, single centre Italy University setting 12 wks. f/u	N=48 F: 12; M: 36 **Mean age (range), yrs.:** 41.2 (10-72) **Mean duration of vitiligo (range), yrs.:** 9 (1-45)	Group A (n=16): MEL 308nm + khellin 4%, once weekly + oral vitamin E, once daily Group B (n=16): MEL 308nm, once weekly + oral vitamin E, once daily Group C (n=16): vitamin E, once daily Patients were treated for 12 wks. *N.B. Other interventions investigated by this study are presented in table 15.*	Repigmentation ≥75% (>75%) at 12 wks. Repigmentation ≥50% (>50%) at 12 wks. Harms: erythema, burning/pain, perilesional hyperpigmentation	Attrition: three patients did not complete the study dues to onset of side effects (one patients) and unresponsiveness (two patients).

Abbreviations: F, female; M, male; MEL, monochromatic excimer light; NB-UVB, narrow band ultraviolet B; NR, not reported; PRP, platelet rich plasma; PUVA, psoralens ultraviolet A; RCT, randomized controlled trial; wks., weeks; yrs., years.

Table 13: Included comparative studies investigating surgical therapies

Study details	Population	Intervention	Outcomes	Comments
Anbar, T. S., T. S. El-Ammawi, et al. (2020). J Cosmet Dermatol.[57] RCT Egypt Hospital 3 mos. post-treatment f/u	N=40 M: 20; F: 20 **Mean (SD) [range] age, yrs.:** Group A, 36.8 (15) [14 – 50]; Group B, 28.3 (13.5) [12-40] **Mean (SD) [range] duration of vitiligo, yrs.:** Group A, 10.3 (7.4) [2-20]; Group B, 5 (2.2) [2 – 10]	Group A (n=20): NCES from blister roofs Group B (n=20): NCES from partial-thickness epidermal cuts	Repigmentation ≥ 75% Repigmentation ≥ 50% Harms: • Hyperpigmentation	**Attrition:** 0%
Awasti, S. (2019). Journal of the European Academy of Dermatology and Venereology: JEADV 33: e237 – 9[58] RCT India University 16 wks. f/u	N=30 F: 14; M: 16 **Mean (SD) age, yrs.:** Group A, 24.87 (7.5); Group B, 24.6 (7.9) **Mean (SD) duration of disease, yrs.:** Group A, 11.2 (9.3); Group B, 10.0 (8.99)	Group A (n=22 lesions): cold trypsinization preparation of autologous non-cultured epidermal cell suspension Group B (n=20 lesions): warm trypsinization preparation of autologous non-cultured epidermal cell suspensions	Repigmentation ≥ 75% (>75%)	**Attrition:** 0%

Study details	Population	Intervention	Outcomes	Comments
Ebrahim, H. M. and W. Albalate (2020). J Cosmet Dermatol: 1-8 [59] RCT, single centre Egypt University 3-mo. post-treatment f/u	N=60 F: 28; M: 32 **Mean (SD) [range], yrs.:** Group A, 36.52 (8.23) [12 – 60]; Group B, 37.12 (9.31) [14 – 58] **Mean (SD) [range] duration of vitiligo, yrs.:** Group A, 3.24 (1.8) [3-6]; Group B, 3.16 (1.02) [4-5]	Group A (n =30): microneedling intervals + tacrolimus 0.1% at 2 wk. intervals Group B (n=30): microneedling at 2 wk. intervals Treatment for 6 mos. *N.B. other interventions investigated in this study are presented in table 9*	Repigmentation ≥ 75% Repigmentation ≥ 50% Harms: • Erythema • Pain • Itching	**Attrition:** 0%
Elshafy Khashaba, S. A. (2018). Journal of the American Academy of Dermatology 79: 365-367.[62] RCT, single centre Egypt University setting 3 mos. f/u	N=40 F: 25; M: 15 **Mean (SD) age, yrs.:** Group A, 25.30 (8.55); Group B, 28.05 (10.12) **Duration of vitiligo, mo.:** Group A, 14.70 (9.50); Group B, 20.30 (14.50)	Group A (n=20): micro-needling once wkly. + NB-UVB Group B (n=20): micro-needling once wkly. Treatment for 3 mos. *N.B. other interventions investigated in this study are presented in table 11*	Repigmentation ≥ 75% Repigmentation ≥ 50%	**Patient satisfaction** Excellent: Group A, n = 8; Group B, n = 5 Fair: Group A, n = 7; Group B, n = 6 Poor: Group A, n = 5; Group B, n = 9
Hamza, A., T. Hussein, et al. (2019). Journal	N=20 F: 9; M: 11	Group A (n=10) NCORSHFS Group B (n=10) NCES	Repigmentation ≥ 75% Repigmentation ≥ 50%	**Attrition:** 0% **Patient satisfaction**

Study details	Population	Intervention	Outcomes	Comments
of cutaneous and aesthetic surgery 12(2): 105-111.[63] RCT, single centre Egypt Hospital setting 3 mos. f/u	Median (range) age, yrs.: Group A, 27 (15 – 45); Group B, 39 (14 – 52)		Harms: • Hyperpigmentation • Mild scarring	Satisfied: Group A, 8/10; Group B, 5/10 Fair: Group A, 2/10; Group B, 3/10 Unsatisfied: Group A, 0/10; Group B, 2/10
Majid, I. (2016). J Cutan Aesthet Surg 9:13-19.[39] Non-randomized, multicentre comparative study India Outpatient 6 mos. f/u	N=170 F: 114; M: 56 **Mean age (SD) [range], yrs.:** group A, 25.98 (8.01) [13-52]; group B, 26.4 (8.81) [14-61] **Duration of vitiligo:** NR **Disease stability:** group A, patients with a disease stability of 6-11 mos. and a lesional stability of >1 yr.; group B, patients with a disease stability >1 yr.	Group A (n=75): Miniature punch grafting (MPG) Group B (n=64): Ultra-thin and split-thickness skin grafting (UTSG and STSG) Group C (n=31): Nonculture epidermal cell suspension technique (NCES) Dermabrasion was conducted but method not stated. Each centre was encouraged to give a fair and equal representation of the interventions to both the groups while recruiting patients for the study.	Repigmentation ≥75% (≥90%) at 6 mos. Repigmentation ≥50% at 6 mos.	This focus of this study was to investigate the impact of disease stability on surgical performance rather than comparing the impact of different surgical techniques on disease. The patients (n=170) were divided into two groups: Group 1 with lesional stability of >1 year but overall disease stability of only 6-11 mos. and Group 2 with overall disease stability of >1 year. The surgical procedures included MPG, UTSG, STSG, and NCES. Each centre was encouraged to give a fair and equal representation to both groups while recruiting patients for the study. **Repigmentation:**

Study details	Population	Intervention	Outcomes	Comments
				○ Repigmentation was assessed and scored from 0 (no repigmentation) to 6 (complete repigmentation). The response was termed as excellent if the score was 5 or 6 (90-100% repigmentation), good if the score was 3 or 4 (50-75% repigmentation), and poor when the score was <3 (<50% repigmentation). ○ Average pigmentation score, group 1, 3.8; group 2, 4.04. ○ Among the 69 responders in group 1, 36.6% cases (30/82) achieved excellent results in the form of near-complete repigmentation whilst good repigmentation (50-75%) was achieved in 47.6% of cases (39/82). ○ Among the 80 responders in group 2, 37.5% cases (33/88) achieved excellent repigmentation whilst 53.4% cases (47/88) achieved good repigmentation. ○ The face and neck area responded most favourably to surgical intervention, with 51.6% lesions (16/31) and 55.9% lesions (19/34) achieving complete repigmentation in Group 1 and Group 2, respectively. The acral lesions were the worst responders, the correlation of the response with the site of lesions was statistically significant (p<0.001).

Study details	Population	Intervention	Outcomes	Comments
				○ Poor response (<50% repigmentation) was seen in some cases with each of the grafting techniques, but the number of non-responders (13.3%) was highest in the MPG group. **Side effects:** Perigraft halo (15 cases), hyperpigmentation (9 cases), graft dislodgement (4 cases), cobblestoning (4 cases), textural irregularity (3 cases) keloid formation (1 case) and infection (1 case).
Thakur, D. S., S. Kumar, et al. (2020). J Eur Acad Dermatol Venereol 34(1): e34-e36.[71] RCT, single centre India Hospital 16 wks. post treatment f/u	N=30 F: 17; M: 13 **Mean (SD) age, yrs.:** Group A, 24.9 (5.9); Group B, 22.7 (5.7) **Mean (SD) duration of vitiligo, yrs.:** Group A, 9.8 (8.0); Group B, 11.0 (4.9)	Group A (n=15): follicular unit extraction Group B (n=15): plucking hair follicles	Repigmentation ≥ 75% (>75%) Repigmentation ≥ 50% (> 50%)	
Thakur, V. (2019). JAMA Dermatology 155: 204-210.[72]	N=40 F: 24; M: 16 **Mean (SD) age, yrs.:** 24.9 (4.0)	Group A1 (n=10): NCES Group A2 (n=10): NCES/NDCS	Repigmentation ≥ 75% (>75%) Repigmentation ≥ 50%	

Study details	Population	Intervention	Outcomes	Comments
RCT, single centre India Outpatient 24 wks. post-treatment f/u	**Mean (SD) duration of vitiligo, yrs.:** Group A1, 6.45 (6.98); Group A2, 5.5 (4.03); Group B1, 8.6 (3.74); Group B2, 12.3 (5.73) Group A (n=20) had disease stability for 3 – 6 mos. Group B (n=20) had disease stability for >12 mos.	Group B1 (n=10): NCES Group B2 (n=10): NCES/NDCS	(> 50%)	

Abbreviations: BG, blister roof grafting; CMT, cultured melanocytes transplantation; F, female; M, male; MPG, Miniature punch grafting; NCES, Non-cultured epidermal cell suspension transplantation; NCORSHFS, non-cultured extracted hair follicle outer root sheath cell suspension; NDCS, non-cultured dermal cell suspension NR, not reported; SD, standard deviation; STSG, split-thickness skin grafting; UTSG, Ultra-thin skin grafting; yrs., years.

Table 14: Included comparative studies investigating skin camouflage therapies

Study details	Population	Intervention & Comparator	Outcomes	Comments
Hosseinkhani, A. (2015). J Evid Based Complementary Altern Med 20: 254-258.[40] RCT, double blind, single centre Iran University 8 wks. f/u	N=30 F: 25; M: 5 **Mean age (SD), yrs.:** group A, 38.93(12.97); group B, 41.06(11.82) **Mean duration of vitiligo:** group A, 10.20(10.55); group B, 9.70(5.71)	Group A (n =18): Sabgh group (herbal formulation) Group B (n=16): Exuviance group (active ingredient is titanium dioxide) Patients were treated for 8 wks.	QoL: DLQI scores at 8 wks.	Attrition: Four patients were lost to follow up as they did not attend the follow up sessions.

Abbreviation: DLQI, dermatology life quality index; F, female; M, male; QoL, quality of life; RCT, randomized controlled trial; SD, standard deviation; wks., weeks; yrs., years.

Table 15: Included comparative studies investigating complementary therapies

Study details	Population	Intervention & Comparator	Outcomes	Comments
Abdelghani, R. (2017). J Cosmetic dermatol.[49] RCT, single centre Egypt University setting 5 mos. f/u	N=80 F: 50; M: 30 **Mean age (SD), yrs.:** group A; 33.90 (11.89); group B, 34.90 (15.39); **Mean disease duration:** <2 years, 34; >2 years, 46	Group A (n=20): CO_2 laser + PRP, same as protocol for group A and B Group B (n=20): PRP, 4 sessions with 3-wk. interval Patients were treated for 2 mos. *N.B. Other interventions investigated by this study are summarised in table 11 and 12.*	Repigmentation ≥75% (>75%) at 5 mos.	Harms: erythema, itching, burning sensation, ecchymosis
Mou, K. H. (2016). Braz J Med Biol Res 49.[50] Open-label RCT, single-centre Hospital China 6 mos. f/u	N=144 F: NR; M: NR **Age (range), yrs.:** 3 – 48 **Duration of disease, yrs.:** 3 – 48	Group A (n=48): OCG + UVB (dosage as for group A and group B) Group B (n=48): OCG, patients >60kg and >12 yrs. received 2 tablets three times daily; patients <60kg and <12 yrs. received 1 tablet three times daily Patients were followed-up for 6 mos. *N.B. Other interventions investigated by this study are summarised in table 11.*	QoL: DLQ at 6 mos.	**Effectiveness rate:** • 87.5% repigmentation rate in group A (42/48) • 75.0% repigmentation rate in group B (36/48) The differences in effectiveness rate between group A and B were significant ($p < 0.05$). **VIDA score:** Score decreased in all groups during treatment, showing both OCG and UVB to be effective. In the 2nd and 6th mos. of treatment, group A scores were significantly lower than group B ($p < 0.05$).

Saraceno, R. (2009). Dermatol Ther 22: 391-394.[38] Non-randomized comparative study, single centre Italy University setting 12 wks. f/u	N=48 F: 12; M: 36 **Mean age (range), yrs.:** 41.2 (10-72) **Mean duration of vitiligo (range), yrs.:** 9 (1-45)	Group A (n=16): MEL 308nm + khellin 4%, once weekly + oral vitamin E, once daily Group B (n=16): MEL 308nm, once weekly + oral vitamin E, once daily Group C (n=16): vitamin E, once daily Patients were treated for 12 wks. *N.B. Other interventions investigated by this study are presented in table 12.*	Repigmentation ≥75% (>75%) at 12 wks. Repigmentation ≥50% (>50%) at 12 wks. Harms: erythema, burning/pain, perilesional hyperpigmentation	Attrition: three patients did not complete the study dues to onset of side effects (one patients) and unresponsiveness (two patients).
Van, T. N. (2019). Open access Macedonian journal of medical sciences 7: 283-286.[73] RCT Italy Hospital 12 wks. f/u	N=62 F: 36; M: 26 **Mean (range) age, yrs.:** 34.5 (18 – 58) **Duration of vitiligo:** NR	Group A (n=35): Vitilinex + NB-UVB 311 nm Group B (n=24): Vitilinex herbal bio-actives alone Treatment for 12 wks. *N.B. other interventions investigated in this study are presented in table 11*	Repigmentation ≥ 75% (>75%) Repigmentation ≥ 50% (> 50%)	
Zhang, C. (2017). J Dermatolog	N=233 F: 142; M:91	Group A (n=80): Yiqiqubai granule 20g twice daily + 308nm laser once a week	Repigmentation ≥ 50% at 6 mos.	

Treat 28: 668-671.[53] Randomized comparative study, single centre study Hospital China 6 mos. f/u	**Mean age (SD), yrs.:** group A, 30.2 (5.4); group B, 31.5(6.3); group C, 27.8 (5.1)	Group B (n=75): Yiqiqubai granule 20g twice daily Patients were treated for 6 mos. *N.B. Other interventions investigated by this study are presented in Table 11.*	Change in QoL at 6-mos. for: embarrassment, dress, social, and work.	

Abbreviations: CBC, complete blood count; CDLQI, children's dermatology life quality index; CO_2, carbon dioxide; F, female; ITT, intention to treat; M, male; MTX, methotrexate; NB-UVB, narrow-band ultraviolet B; OCG, oral compound glycyrrhizin; OMP, oral minipulses; PRP, platelet rich plasma; RCT, randomized controlled trial; SD, standard deviation; UVB, ultraviolet B; VIDA, vitiligo disease activity score; vitiligo disease VASI, vitiligo area scoring index; VETF, Vitiligo European Task Force; yrs., years.

Table 16: Included comparative studies investigating depigmentation therapies

Study details	Population	Intervention & Comparator	Comments
El-Mofty, M., W. Z. Mostafa, et al. (2019). Dermatol Ther 32(5): e13052.[61] Prospective cohort Egypt Outpatient 6 mos. f/u	N=40 F: 27; M: 13 **Mean (range) age, yrs.:** Group A, 37 (13 – 65); Group B, 43 (17 – 55)	Group A (n=20): facial depigmentation (TCA peel 25%/TCA peel 50%/Qs Nd:YAG laser) Group B (n=20): extra-facial depigmentation (Phenol peel 88%/Cryotherapy/Qs Nd:YAG laser) Treatment for 3 mos.	Depigmentation > 90% High patient satisfaction

Abbreviations: F, female; f/u, follow-up; M, male; mos., months; Nd: YAG, neodymium-doped yttrium aluminum garnet; TCA, trichloroacetic acid

Appendix F: Comparative studies with non-extractable data

Table 17: Summary of comparative studies with non-extractable data for topical therapies

Study details	Population	Intervention & Comparator	Comments
Ameen, M. (2001). Br J Dermatol 145: 476-479.[41] Non-randomized comparative study UK Outpatient Mean: 6 mos. f/u	N=26 F: 16; M: 10 **Mean age (range), yrs:** 28 (5-61) **Mean (range) duration of vitiligo, yrs:** 3.8 (1-11)	Group A (n=22): Calcipotriol Group B (n=4): Calcipotriol + PUVA Treatment was stopped after complete repigmentation or after 3 mos. if the vitiliginous lesions showed no evidence of repigmentation. By the end of the study, all patients had been on treatment with topical calcipotriol for 3-9 mos. (6 mos.)	**Repigmentation** **Group A:** ○ Repigmentation ≥ 50%, n (%): 12(55) ○ Complete repigmentation or >90% improvement, n (%): 5(23) **Group B:** ○ Only four patients received combination therapy, one of the four patients showed >90% improvement after 9 mos. of therapy. Response to treatment was better in patients with vitiligo < 5 years duration and where it was less extensive (<10 %).

Abbreviations: BSA, body surface area; F, female; M, male; mos., months; NR, not reported; PUVA, psoralens ultraviolet A; RCT, randomized controlled trial; UK, United Kingdom; wk., week; yrs., years

Table 18: Summary of comparative studies with non-extractable data for light therapies

Study details	Population	Intervention & Comparator	Comments
Westerhof, W. (1997). Arch Dermatol 133: 1525-1528.[33] Non-randomized blinded comparative study The Netherlands Medical centre 4 mos. and 12 mos.	N=281 F:182; M:99 **Mean age (SD) [range], yrs.:** Group A, 36.7 (15.3) [8-63]; Group B, 36.0 (16.5) [7-70] **Mean duration of vitiligo, mos.:** Group A, 11.7 (5.6); Group B, 13.8 (10.0)	Group A (n=106): topical PUVA (n = 28) or 311-nm UV-B radiation (n = 78), patients were treated twice weekly for 4 mos. Group B (n = 175): 311-nm UV-B, patients were treated twice weekly for 12 mos.	**Repigmentation in group A:** During 4 mos. of treatment therapy, n (%): ○ Topical PUVA, 13 (46) ○ 311-nm UV-B radiation, 52 (67) **Repigmentation ≥75% (>75%) in group B, n (%):** ○ 3 mos., 5 (8) ○ 6 mos., 11 (42) ○ 9 mos., 18 (49) ○ 12 mos., 32 (63) Patients in Group A were treated twice weekly for 4 mos. and evaluated at the end of the 4 mos.' treatment period; patients in group B were treated for 12 mos. and evaluated after 3, 6, 9, and 12 mos. of treatment.
Gianfaldoni, S. (2018). OAMJMS 6: 46-48.[51] Retrospective comparative study, multicentre Hospital Italy, Germany, Croatia, Bulgaria, America, and Australia 36 wks. f/u	N=67 F: 44; M: 23 **Age (range), yrs.:** 25 – 61 **Duration of vitiligo:** stable or active vitiligo for more than 2 yrs and less than 10 yrs.	Group A (n=9): NB-UVB micro-phototherapy + tofacitinib Group B (n=58): NB-UVB micro-phototherapy Patients were treated once every three wks. for a total of 12 sessions.	Side effects were not observed in both groups **Repigmentation:** 92% repigmentation (nearly complete repigmentation) in all 9 patients in group A >75% repigmentation obtained in 42 patients (72%) in Group B

<table>
<tr><th>Study details</th><th>Population</th><th>Intervention & Comparator</th><th>Comments</th></tr>
<tr><td>Ullah, G. (2017). JPAD27: 232-237.[52]

RCT, single centre

Hospital

Pakistan

3 mos. f/u</td><td>N=94
F: 59; M: 35
Mean (SD) [range] age, yrs.: 28.59 (8.86) [15-51]
Duration of vitiligo, ≤ 5.00 (yrs.): group A, 4; group B, 4
Duration of vitiligo, > 6 (yrs.): group A, 43; group B, 43</td><td>Group A (n=47): tacrolimus + NB-UVB

Group B (n=47): NB-UVB

Patients were treated for 3 mos.</td><td>Repigmentation:

28% achieved >75% repigmentation at 3-mo. follow-up – unclear if this is for a specific arm or in total for the study.</td></tr>
<tr><td>Uitentuis, S. E., V. S. Narayan, et al. (2019). J Dermatolog Treat 30(6): 594-597.[75]

Retrospective cohort

Netherlands

University setting

3 mos. f/u</td><td>N=92
F: 54; M: 38
Mean (SD) age, yrs.:
Group A, 43 (13) [17 – 68]; Group B, 46 (14) [21 – 74]
Duration of vitiligo > 5 yrs.:
Group A, 56%; Group B, 66%</td><td>Group A (n=45): NB-UVB thrice wkly. + topical treatment

Group B (n=47): NB-UVB twice wkly. on non-consecutive days</td><td>Median % repigmentation (IQR) at different body sites:

<table><tr><th>Site</th><th>Group A</th><th>N</th><th>Group B</th><th>N</th><th>P - value</th></tr><tr><td>Face</td><td>60 (6 – 80)</td><td>28</td><td>60 (6 – 80)</td><td>40</td><td>0.20</td></tr><tr><td>Neck</td><td>40 (30 – 70)</td><td>19</td><td>40 (30 – 70)</td><td>25</td><td>0.79</td></tr><tr><td>Trunk</td><td>30 (10 – 55)</td><td>30</td><td>30 (10 – 55)</td><td>33</td><td>0.50</td></tr><tr><td>Arms</td><td>40 (10 – 60)</td><td>29</td><td>40 (10 – 60)</td><td>32</td><td>0.49</td></tr><tr><td>Hands</td><td>10 (0 – 30)</td><td>31</td><td>10 (0 – 30)</td><td>32</td><td>0.37</td></tr><tr><td>Legs</td><td>35 (6 – 58)</td><td>24</td><td>35 (6 – 58)</td><td>33</td><td>0.78</td></tr><tr><td>Feet</td><td>0 (0 – 15)</td><td>17</td><td>0 (0 – 15)</td><td>25</td><td>0.60</td></tr></table></td></tr>
</table>

Abbreviations: CI, confidence interval; F, female; IQE, interquartile range; M, male; NB-UVB, narrow band ultraviolet B; PUVA, psoralen ultraviolet A; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; wks., weeks; yrs., years.

Table 19: Summary of comparative studies with non-extractable data for psychological therapies

Study details	Population	Intervention & Comparator	Comments
Papadopoulos, L. (1999). Br J Med Psychol 72: 385-396.[42] RCT, single centre UK University setting 5 mos. f/u	N=16 F: 8; M: 8 **Mean age (SD), yrs.:** 39.3 (NR) **Mean duration of vitiligo, yrs.**: 14.2	Group A: Cognitive behavioural therapy, one session conducted weekly by a psychologist over an 8-wk period. Group B: No counselling and no change to conventional treatment status (no medical treatments or PUVA).	Of the 16 participants only 12 were eligible to have the progression of their vitiligo assessed through photographs as the other four were receiving PUVA treatment. In total, 11 of the 12 patients agreed to be photographed. **Change in lesion size:** ○ Independent clinicians (dermatologist and a general practitioner) were asked to observe the before and after photographs of the 11 participants and were blinded to which photographs were taken before and after treatment; both clinicians indicated that they observed changes in the same five cases. Furthermore, the same five cases were identified as having changed by the three researchers who also examined the photographs. ○ In three cases from group A, the clinicians indicated that they observed an improvement (i.e. a reduction in the size of vitiligo lesions) and in two cases from the control group they observed a deterioration (i.e. an increase in size of the lesions). ○ Results of the likelihood ratio test suggested that the change in size of the lesions was statistically significant.
Papadopoulos, L. (2004). Dermatol Psychosom 5: 172-177.[43] RCT, multicentre UK Hospital and community 12 mos. f/u	N=44 F: 31; M: 13 **Mean age (SD), yrs.:** group A, 36.39 (12.05); group B, 35.85 (11.72); control, 37.71 (11.09) **Duration of vitiligo, yrs.:** NR	Group A: CBT, one session conducted weekly by a psychologist over an 8-week period. Group B: Person-centred treatment group (patients did not receive direct intervention from the therapist). This was based on concepts from humanistic psychology. Group C: Control: no counselling and no change to treatment status.	○ CBT and patient centred groups made significant improvements only in general health. For the CBT groups, improvements were noticeable directly post-treatment and maintained over the duration of the follow ups. ○ For the patient-centred groups, improvements were only visible at 6-mo. and 12-mo. follow-up, but no improvement was found immediately after therapy. ○ There were no significant changes in the responses obtained from the control group on any of the above variables at any time point.

Study details	Population	Intervention & Comparator	Comments
Shah, R. (2014). Br J Dermatol 171: 332-337.[44] RCT, single centre UK Community 8 wks. f/u	N=75 F: NR; M: NR **Age range, yrs.:** 18-65 **Duration of vitiligo:** NR	Group A: CBSH+[1] Group B: CBSH Group C: No intervention	**bFNE score:** ○ A higher percentage of participants showed RCS[2] in the CBSH+ group (24%) than in the other two groups (8% in the CBSH group and 0% in the control group). **HADS anxiety, HADS depression, and DAS-24:** ○ There was no statistically significant difference between the groups; there was no difference between the percentage of participants who showed RCS improvement in the CBSH+ group, and the percentage of participants who showed improvements in the CBSH and the control groups.

Abbreviations: bFNE, brief fear of negative evaluation scale; CBSH, Cognitive behavioural self-help intervention; CBSH+, Cognitive behavioural self-help enhanced; CBT, cognitive behavioural therapy; DAS, Derriford appearance scale; DLQI, Dermatology Life Quality Index; F, female; HADS, Hospital Anxiety and Depression scale; M, male; NR, not reported; PUVA, psoralens ultraviolet A; RCS, reliable and clinically significant improvement; RCT, randomized controlled trial; yrs., years.

[1]CBSH augmented with implementation intentions, this provided specific if-then plans aimed at increasing the use of the interventions. For example, how to respond to feeling anxious at a party or whilst shopping.

[2] If scores were more than the clinically significant value, then they were classified as a reliable and clinically significant improvement.

Table 20: Summary of comparative studies with non-extractable data for skin camouflage therapies

Study details	Population	Intervention & Comparator	Comments
Tanioka, M. (2010). J Cosmet Dermatol 9: 72-75.[45] Non-randomized comparative study, bi-centric Japan Clinic in a hospital setting	N=144 F: group A, 48%; group B, 45%; M: group A, 52%; group B, 55% **Mean age (SD) [range], yrs.:** group A, 48.1; group B, 40.8 **Mean duration of vitiligo, mos.:** group A, 19.5; group B, 17.5	Group A: Skin camouflage lessons provided bimonthly by specialist volunteers for camouflage for pigmentary disorders. The lessons were conducted one-to-one. Group B: Without skin camouflage lessons.	DLQI scores, the higher the score the more the QoL is impaired. **QoL:** ○ Group A, DLQI scores improved from 5.90 to 4.48; group B, DLQI scores changed from 3.18 to 4.36. The difference between group A and group B was significant ($p<0.005$). ○ When patients without exposed lesions were excluded (N=27), camouflage was still associated with improvement of DLQI scores ($p = 0.01$). ○ Group A showed statistically significant improvement in “symptoms and feelings” when compared with that of patients in group B ($p = 0.004$).

Study details	Population	Intervention & Comparator	Comments
1 mo. f/u			

Abbreviations: F, female; SD, standard deviation; DLQI, Dermatology Life Quality Index.

Appendix G: Narrative findings from within-patient studies

Table 21: Summary of within-patient studies investigating topical therapies

Study details	Population	Intervention & Comparator	Comments
Abd-Elazim, N. E., H. A. Yassa, et al. (2019). J Cosmet Dermatol 1-9[110] Within-patient RCT, single-centre Egypt Hospital 3 mos. post-treatment f/u	N=35 F: 25; M: 10 **Mean (SD) [range] age, yrs.:** 36 (11) [8 – 59] **Mean (SD) [range] duration of vitiligo, yrs.:** 5 (4.3) [1 – 10]	Group A (35 patches): tacrolimus 0.03% ointment once daily Group B (35 patches): tacrolimus 0.03% ointment twice daily + microdermabrasion Group C (35 patches): petrolatum (placebo) Treatment for 3 mos.	**Repigmentation ≥ 50 – 75%** Group A, 2.9%; Group B, 17.2% **Repigmentation ≥ 75 - 100%** Group A, 0%; Group B, 11.4%
Anbar, T. S. (2015). Int J Dermatol 54: 587-593.[77] Within-patient RCT, L/R comparison single centre Egypt Hospital 6 mos. f/u	N=22 Mean (SD) [range] age, yrs: 15.5 (11.5) [6-55] Mean (SD) [range] duration of vitiligo, mos.: 27.5 (40) [3-180]	Group A: In each patient, one side was treated with latanoprost (LT) while the other side received placebo (saline) to evaluate the effect of LT. Group B: In each patient, one side was treated with LT while the other side was exposed to NB-UVB. Before exposure to NB-UVB, the LT-treated area was wrapped with a tight thick dressing.	**Repigmentation:** ○ Six of the 14 patients treated with LT alone on one side from Group A and B achieved >75% repigmentation ○ There was a statistically significant improvement in lesions treated with a combination (LT + NB-UVB) compared with NB-UVB alone ($p<0.05$) **Follow-up:** ○ Follow-up was done at 6 mos. after the termination of the trial for the persistence

Study details	Population	Intervention & Comparator	Comments
		Group C: In each patient, one side was treated with a combination of LT and NB-UVB while the other side was exposed to NB-UVB only. On days of radiation, the topical application was applied following NB-UVB exposure to avoid their barrier and/or photosensitive effect if any.	of pigmentation, recurrence or development of any side effects ○ Of the 14 patients who achieved >75% repigmentation, two patients were missed in the follow-up; the remaining 12 patients were followed up for 6 mos. ○ Overall, 3 of 12 patients experienced disease activity in the form of the appearance of new lesions and partial loss of gained repigmentation and 9 of 12 patients retained their achieved pigmentation until the end of the 6-mo. follow-up period.
Asilian, A. (2009). JPAD 19: 151-157.[78] Within-patient RCT, R/L comparison, single centre Iran Outpatient 3 mos. f/u	N=37 F: 21; M: 16 **Mean age, yrs:** 27 **Mean duration of vitiligo, mos.:** 4 **Mean area of lesions (SD), cm^2:** Group A, 15.48 (8.40); Group B, 13.92 (8.75) **Mean duration of vitiligo, mos.:** 4	Group A: Clobetasol 0.05% + oestrogen 0.625% cream Group B: Clobetasol 0.05% Patients were treated for 3 mos.	R/L side of the body; one side of the body was treated with clobetasol only for 3 mos. whilst the other side was treated with clobetasol plus oestrogen. **Side effects:** ○ In group B, 4 cases of erythema and telangiectasia were observed. But these complications resolved after a 3-mo. follow-up. ○ Group A did not have side effects such as atrophy, erythema, and telangiectasia. **Mean (SD) disease area, cm^2:** ○ Group B: before treatment, 13.92 (8.75); after treatment, 10.56 (7.05). p = 0.010. ○ Group A: before treatment, 15.48 (8.40); after treatment, 10.19 (6.49). p = 0.013. **Perifollicular pigmentation score:**

Study details	Population	Intervention & Comparator	Comments
			○ At the end of treatment, both groups showed considerable improvement in the perifollicular score. $p < 0.05$. ○ Mean (SD) score: group B 1.41 (0.50); group A, 2.10 (0.75). $p < 0.001$.
Ermis, O. (2001). Br J Dermatol 145: 472-475.[79] Within-patient RCT, L/R comparison, single centre Turkey Setting, NR 8 wks. f/u	N=27 F: 9; M: 18 **Mean age (SEM), yrs:** 29.8 (13.5) **Mean (SEM) duration of vitiligo, yrs:** 7.5 (4.8) **Mean affected BSA (SEM), %:** 14.8 (9.1)	Group A: Clacipotriol + PUVA Group B: Placebo + PUVA Patients were treated for 8 wks.	Attrition: eight patients failed to complete the study. **Initial repigmentation:** ○ In most cases (23 from group A and 17 from group B), it occurred between 4 and 8 wks. of treatment. **Complete pigmentation (75%-100% repigmentation):** ○ Seventeen in group A (63%) and four in group B (15%). ○ In six patients it occurred on both sides and at the same time.
Clayton, R. (1977). Br J Dermatol 96: 71-73.[80] Within-patient RCT, single centre England Hospital 4 mos. f/u	N=25 F: NR; M: NR **Age:** NR **Duration of vitiligo:** NR	Group A: Clobetasol propionate 0.05% cream Group B: placebo cream Patients were directed to apply the creams thinly at night and morning.	**Attrition:** two patients did not complete the trial

Study details	Population	Intervention & Comparator	Comments
Eryilmaz, A. (2009). J Eur Acad Dermatol Venereol 23: 1347-1348.[81] Within-patient RCT, double-blind, single centre Turkey Hospital 8 wks. f/u	N=16 F: 11; M: 5 **Mean age (range), yrs:** 26.8 (4– 55) **Mean duration of vitiligo (range), yrs:** 5.5 (1-26)	Group A: Pimecrolimus (1%) twice daily for 8 wks. Group B: Clobetasol (0.05%) twice daily for 8 wks. Patients were also instructed to apply sunscreen	Attrition: two patients lost to follow-up. • Repigmentation ≥ 75% (>75%) at 8 wks. RR=0.25 SE=0.866 P value = 0.1094 • Repigmentation ≥50% (>50%) at 8 wks. RR=0.286 SE=0.598 P value = 0.0363 **% mean repigmentation:** ○ Group A, 32.1% ○ Group B, 57.7% <u>Dichotomous outcomes with no/insufficient raw data provided:</u> **Side effects:** ○ Side effect was observed in three patients (atrophy in one lesion, atrophy and telangiectasia in one lesion, atrophy and acneiform changes in one lesion) in group B, but no adverse effect with group A.
Hartmann, A. (2008). Acta Derm Venereol 88: 474-479.[82] Within-patient, non-randomized L/R comparison study, single centre Germany	N=31 F: 24; M: 7 **Mean age (range), yrs:** 43.7 (19-65) **Mean duration of vitiligo (range):** 15.8 yrs. (8 mos. to 40 yrs.)	Group A: Tacrolimus 0.1% ointment applied twice daily to the depigmented lesions of the face and neck as well as of the right upper and lower extremity. Group B: On the left side of the limb a bland emollient was used as placebo. In some patients (n =20), occlusive overnight dressing (polyrthylene foil/polyurethane	**Repigmentation:** ○ Group A: at 12 mos., 10 of the 17 patients who showed repigmentation on the face achieved >75% repigmentation. ○ Those with longer disease duration > 10 yrs. had greater overall mean (SD) repigmentation of lesions of the face and arms 49.7% (37.9) compared with 14.7% (27.3) in those with a disease duration < 10 yrs. (p = 0.0009).

Study details	Population	Intervention & Comparator	Comments
Dermatology department of a university 12 mos. f/u		foil/hydrocolloid) on the right arm and leg was used in previously defines areas. Patients were treated for 6 mos.; treatment was stopped if no repigmentation was observed. The responding regions were treated continuously for 12 mos.	○ Occlusion with polyurethane foil or hydrocolloid dressing showed moderate to excellent repigmentation. Repigmentation with hydrocolloid dressing started earlier, mean (SD): 11.3 wks. (3.4) compared with polyurethane, 29.3 wks. (4.6); p < 0.0001 **Side effects:** ○ Side effects were documented in 80% of patients ○ Side effects associated with tacrolimus 0.1% ointment included transient facial flushing, enhanced heat intolerance, burning, mild pruritus, and mild perioral folliculitis ○ Facial flushing occurred irrespective of whether tacrolimus ointment was applied to the face or not ○ None of the side-effects led to discontinuation of therapy **QoL:** ○ The mean (SD) [range] DLQI score was 12.4(6.5) [2–27] before treatment and decreased to 9.3 (5.6) [1–23] after 12 mos. of therapy, indicating statistically significant improvement of QoL (p = 0.001) ○ In patients with moderate to excellent (25-100% repigmentation) the mean (SD) DLQI score at 12 mos. was lower, 8.6 (4.9), in contrast to 10.3 (6.9) for patients in the group treated without success.
Juan, D. (2011). J Dermatol 38: 1092-1094.[83]	N=9 F: NR; M: NR **Age range, yrs:** 2-60	Group A: 0.1% tacrolimus ointment twice daily Group B: mometasone furoate cream once daily	Two studies were conducted, a non-comparative study was included in this publication (see

Study details	Population	Intervention & Comparator	Comments
Within-patient L/R comparison study, single centre China Hospital 3 mos. f/u		Patients were treated for 3 mos.	Appendix H: **Narrative findings from non-comparative studies**). **Repigmentation:** ○ Group A: five patients (56%) ○ Group B: five patients (56%)
Kandil, E. (1974). Br J Dermatol 91: 457-460.[84] Within-patient RCT L/R comparison, double-blind, single centre Kuwait Hospital 4 mos. f/u	N=19 F: NR; M: NR **Mean age, yrs:** NR **Mean duration of vitiligo:** NR	Group A: Betamethasone (0.1%), twice daily Group B: Placebo (unmedicated base), twice daily Patients were treated for 4 mos.	Attrition: two patients lost to follow-up. <u>Dichotomous outcomes with no/insufficient raw data provided:</u> ○ Fifteen cases were cured or improved in group A. ○ Complications of treatment in group A were limited to hypertrichosis in two patients and localised acneiform eruption in 3 other cases. ○ There were no patients who achieved repigmentation with the unmedicated base
Lubaki, L. J. (2010). Arch Dermatol Res 302: 131-137.[85] Within-patient RCT, double-blind placebo controlled, single centre Belgium Hospital	N=40 F: 25; M: 15 **Mean age (range), yrs**: 44 (14-68) **Median duration of vitiligos (range), yrs**: 13 (1-39)	Group A: Tacrolimus (0.1%), twice daily Group B: Placebo, twice daily Patients were treated for 7 mos.	Two prospective studies were conducted; a prospective case series was included within this publication (see non-comparative studies table). **Repigmentation:** ○ Of the 20 lesions treated, 16 (80%) achieved some degree of pigmentation versus 11 (55%) assigned to the vehicle. The effectiveness of tacrolimus was statistically significantly higher ($p < 0.05$) than placebo, McNemar paired t test.

Study details	Population	Intervention & Comparator	Comments
7 mos. f/u			**Side effects:** ○ Tacrolimus was well tolerated except for transient pruritus in the treated areas of four patients.
Naini, F. F. (2012). J Res Pharm Pract 1: 77-80.[86] Within-patient RCT, double-blind, placebo controlled single centre Iran Clinic 6 mos. f/u	N=23 F: 20; M: 3 **Age:** NR **Duration of vitiligo:** all patients included had bilateral vitiligo for at least 12 mos.	Group A: Pseudocatalase/superoxide dismute gel Group B: Placebo gel Patients were treated for at least 6 mos.	Patients were treated and followed up for 6 mos. **Surface area of vitiligous regions:** ○ The decrease in the mean extent of vitiligo lesions' area was not statistically significant during the study period in both groups. **Side effects:** ○ There were no side effects seen in both groups.
Radakovic, S. (2009). J Eur Acad Dermatol Venereol 23: 951-953.[87] Within-patient RCT, single centre Austria Hospital 6 mos. f/u	N=15 F: 10; M: 5 **Mean age (range), yrs.**: 32 (10-61) **Mean duration of vitiligo (range):** 5.1 yrs (9 mos.- 30 yrs.)	Group A: Tacrolimus (0.1%), twice daily Group B: Tacrolimus (0.1%), once daily Group C: No treatment Patients were treated for 6 mos.	Patients with two lesions similar in size, localization and evolution were selected and allocated by computer-generated randomisation list to treatment with once or twice-daily application of 0.1% tacrolimus over a total period of 6 mos. **Degree of repigmentation at 6 mos.:** **Group A** ○ Some repigmentation in 10 of 15 (67%) treated lesions; only two lesions (13%) showed an excellent response (76-100%); four lesions (27%) showed a moderate or poor response. ○ Five lesions (33%) remained unaltered.

Study details	Population	Intervention & Comparator	Comments
			○ Twice daily treatment revealed a statistically significantly better treatment outcome for twice daily tacrolimus than for the untreated control (p = 0.016). **Group B** ○ Some repigmentation in 7 of 15 (46%) treated lesions; of these, 2 (13%) and 5 (33%) had moderate (26%-50%) and poor (1-25%) response. ○ Moderate response (26-50%) occurred in one untreated lesion while the other nine remained unchanged. The difference in therapeutic efficacy between twice daily and once daily tacrolimus remained below statistical significance (p = 0.055); no difference in efficacy was found between once daily tacrolimus and no treatment.
Silpa-Archa, N. (2016). Dermatologica Sinica 34: 177-179.[100] Within-patient RCT Thailand Hospital setting 6 mos. f/u	N=20 F: 17; M: 1 **Mean age (SD), yrs.:** 46.8 (15.60) **Mean (SD) duration of vitiligo, mos.:** 25 (18)	Group A: 0.1% tacrolimus ointment, twice daily Group B: 0.1% mometasone furoate, twice daily Patients were treated for 6 mos.	Repigmentation ≥75% (>75%) at 6 mos. Group A: 11% Group B: 11% Repigmentation ≥50% (>50%) at 6 mos. Group A: 22% Group B: 33% Harms: telangiectasia was present in six cases in group B and no cases in group A (p = 0.03), burning and stinging present in both groups
Westerhof, W. (1999). Arch Dermatol 135: 1061-1066.[88]	N=135 F: 93; M: 42 **Age (range), yrs:** 18-80	Group A: FP alone vs. FP + UV-A Group B: UV-A alone vs. FP + UV-A	Patients were randomized to Group A or Group B. Patients were followed up over 9 mos.; in

Study details	Population	Intervention & Comparator	Comments
Within-patient RCT, L/R comparison, single centre The Netherlands Academic medical centre 9 mos. f/u	**Duration of vitiligo (range), yrs:** 1-50	Patients were treated for 9 mos.	group A, 23 patients withdrew and, group B, 16 patients withdrew. **ITT repigmentation results at 9 mos., mean (SD) [range], %:** ○ Group A: FP alone, 7.73 (20.04) [0.0-100.00]; FP + UV-A, 23.64 (35.67) [0.0-100.0] p < 0.001 compared with FP alone. ○ Group B: UV-A alone, 9.03 (21.68) [0.0-95.0]; FP + UV-A, 25.41 (35.04) [0.0-1.00] p<0.001 compared to UV-A alone. **ITT successful (>75% repigmentation) treatment at 9 mos., number of patients:** ○ Group A: FP alone, 2; FP + UV-A, 10 (p = 0.008). ○ Group B: UV-A alone, 3; FP + UV-A, 8 (p = 0.06). **Side effects:** ○ No patient, irrespective of whether they withdrew experienced adverse effects.

Abbreviations: BSA, body surface area; F, female; FP, fluticasone propionate; ITT, intention to treat; LT, latanoprost; M, male; NB-UVB, narrow band UVB; NA; not applicable; NR, not reported; PUVA, psoralen and UVA; QoL, quality of Life; RCT, randomized controlled trial; RR, risk ratio; SE, standard error; SD, standard deviation; SEM, standard error of mean; UVA, ultraviolet A; UVB, ultraviolet B; wks.; weeks; yr., year.

Table 22: Summary of within-patient studies investigating combination therapies

Study details	Population	Intervention & Comparator	Comments
Ibrahim, Z. A. (2019). Journal of Cosmetic	N=25 F: 13 M: 12 **Mean (SD) age, yrs.:** 23.12 (12.38)	Group A (25 patches): microneedling + tacrolimus, treatment every 2 wks.	**Repigmentation 76 – 100%** Group A, 15/25 (60%); Group B, 8/25 (32%) **Repigmentation 51 – 75%**

Study details	Population	Intervention & Comparator	Comments
Dermatology 18: 581-588.[125] Within-patient non-randomized comparative, single centre Egypt University 3 mos. post-treatment f/u	**Duration of vitiligo, yrs.:** <1 yr., 3/25; 1 – 5 yrs., 15/25; >5 yrs., 7/25	Group B (25 patches): calcipotriol + betamethasone Treatment for 6 mos. (12 sessions)	Group A, 0/25 (0%); Group B, 3/25 (12%) **Patient satisfaction:** Group A, 14/25 (56%); Group B, 8/25 (32%) **Adverse effects:** Group A: pain (14/25), erythema (14/25), exfoliations (7/25); Group B: pain (14/25), erythema (13/25), exfoliations (0/25)
Korobko, I. V. (2016). Dermatol ther 29: 437-441.[101] Within-patient, *non-randomized* comparative study Russia University setting 3 mos. f/u	N=24 F = 21; M= 3 **Mean age (SD) [range], yrs.:** 40.3 (10.0) [24-66] **Mean (SD) duration of vitiligo, yrs.:** 12.1 (8.6) [3-36]	Group A: microneedling (0.5mm needle) + latanoprost 0.005% solution Group B: microneedling (0.5mm needle) + tacrolimus 0.1% ointment NB-UVB phototherapy (three times a week) Patients were treated for 3 mos.	Attrition: two patients were lost to follow-up Repigmentation: >75% repigmentation: group A, 7/24; group B, 1/24, p= 0.0459 >50% repigmentation: group A, 10/24; group B, 8/24 Neither of the patients reported adverse effects of the administered treatment.

Study details	Population	Intervention & Comparator	Comments
Li, L. (2015). Dermatol Ther 28: 131-134.[89] Within-patient RCT, L/R comparison, single centre China Hospital 6 mos. f/u	N=25 F: 13; M: 12 **Age range, yrs:** 21-63 **Duration of vitiligo:** NR	Group A: Fractional CO_2 laser + topical compound betamethasone solution + NB-UVB Group B: Fractional CO_2 laser + NB-UVB Patients were treated for 6 mos.	**Repigmentation:** ○ At 3 mos., > 50% repigmentation was seen in 10 (40%) patients on the treatment side and more than two (8%) patients on the control side, p = 0.057. ○ At 6 mos., > 50% repigmentation increased to 11 (44%) patients, this was statistically significantly higher than the two (8%) seen on the control side, p = 0.042. ○ At 3 mos., >75% repigmentation was seen in two patients on the treatment side and zero patients on the control side; this remained the same at 6 mos. Statistical significance was not reported. **Side effects:** ○ No patients developed noticeable adverse events. All patients experienced moderate pain during the laser treatment as well as slight burning sensation, and erythema, oedema after laser treatment.
Liu, L., Y. Wu, et al. (2019). J Dermatolog Treat 30(4): 320-327.[126] Within–patient RCT, single centre China Hospital	N=289 F: 191; M: 98 **Median (range) age, yrs.:** 31 (25 – 41) **Median (range) duration, mos.:** 48 (24 – 120)	Group A: ablative fractional CO_2 + betamethasone dipropionate cream (once a month) + NB-UVB (3 times weekly) Group B: betamethasone dipropionate cream (once a day) + NB-UVB (3 times weekly) Treatment for 5 mos.	**Attrition:** 163/289 (physician discontinuation, 126/289; patient choice, 25/289; adverse event, 2/289; lost to follow-up, 10/189) **Repigmentation 50 – 98%** Group A, 18/289; Group B, 5/289

Study details	Population	Intervention & Comparator	Comments
1 mo. Post-treatment f/u			
Mina, M. (2018). J Cosmet Dermatol 17: 744-751.[102] Within-patient, non-randomized comparative study Egypt Outpatient clinic 3 mos. after the last session	N=25 F: 15; M: 10 **Mean age (SD) [range], yrs.:** 26.44 (15.26) [10.0 – 64.0] **Duration of vitiligo, n (%):** <5 yrs., 13 (52.0); >5 yrs., 12(48.0)	Group A: microneedling (dermapen) + 5-flurouracil Group B: microneedling (dermapen) + tacrolimus Procedure was repeated every 2 weeks for a maximum 6 mos. (12 sessions)	**Repigmentation:** >75% repigmentation: group A, 12/25 patients; group B, 4/25 patients >50% repigmentation: group A, 13/25 patients; group B, 10/25 patients **Side effects, n (%):** Group A, Hyperpigmentation 4 (16); inflammation 3 (12); ulceration 1 (4) Group B, no complications in all patches 25 patches Difference between group A and group B (p = 0.004)
Wen, X. (2019). Dermatologic Therapy 32.[127]	N=21 F: 8; M: 13 **Mean age, yrs.:** NR	Group A: fractional CO_2 laser + 0.1% tacrolimus 0.1% ointment + 308nm excimer laser	**51% - 75% repigmentation** Group A, 4/21; Group B, 3/21 **75 – 100% repigmentation**

Study details	Population	Intervention & Comparator	Comments
Within-patient RCT, single centre China Hospital 6 mos. f/u	**Duration of vitiligo, mos.:** 7.6 (6.3)	Group B: tacrolimus 0.1% ointment + 308 nm excimer laser Treatment for 6 mos.	Group A, 2/21; Group B, 2/21 **Side effects:** Erythema and perilesional hyperpigmentation observed in some CO_2 treated patches, this was reduced afterwards.

Study details	Population	Intervention & Comparator	Comments
Vachiramon, V. (2016). Lasers Surg Med 48: 197-202.[90] Within-patient RCT, comparison study, single centre Thailand Outpatient 3 mos. post treatment f/u	N=26 F: 15; M: 11 **Mean age (SD), yrs:** 51.2 (8.5) **Mean duration of vitiligo (SD), mos.:** 70.58 (25.69)	Group A: fractional CO_2 laser + NB-UVB phototherapy + 0.05% clobetasol propionate cream Group B: NB-UVB phototherapy + 0.05% clobetasol propionate cream The phototherapy sessions were given twice weekly for 20 sessions on non-consecutive days	Attrition: one patient was lost to follow-up. In total, 26 paired lesions on both hands and fingers were treated. **Repigmentation:** ○ At follow-up, six vitiligous lesions (23.1%) in group A achieved >50 % repigmentation compared with one lesion (3.9%) in group B (p = 0.065). ○ None of the lesions in both groups achieved 100% repigmentation at 3 mos. ○ When the lesions on different areas of the hand (dorsal hand vs. fingers) were considered separately, group A showed a statistically significantly higher mean improvement score from baseline than group B in both areas. In the dorsal hand, mean improvement score for group A vs. group B was 1.67 (1.45) vs. 0.67 (1.13), p = 0.0053; in the fingers, mean improvement score for group A vs. group B was 0.80 (1.08) vs. 0.28 (0.61), p = 0.0048. **Side effects:** ○ The most common adverse event was pain, this was observed more commonly in group A (25 of 26 lesions) compared with group B (12 of 26 lesions), the mean pain score was 4.49 (2.42) in group A versus 1.12 (2.09) in group B (p < 0.001).

Abbreviations: CO_2, carbon dioxide; F, female; M, male; LT, latanoprost; NR, not reported; SD, standard deviation; NB-UVB, narrow band ultraviolet B; UVB, ultraviolet B.

Table 23: Summary of within-patient studies investigating light therapies

Study details	Population	Intervention & Comparator	Comments
Abd El-Samad, Z. (2012). J Dermatolog Treat 23: 443-448.[91] Within-patient non-randomized, single centre Outpatient clinic Egypt 6 mos. f/u	N=60 F: 34; M: 26 **Mean age (SD) [range], yrs:** 28 (5.65) [18-35]	Group A: NB-UVB + intradermal injection of 5FU every 2 wks. Group B: NB-UVB only Patients were treated for 4 mos.	**Repigmentation:** ○ The overall qualitative response was better in the 5-FU side than control side; the quantitative response was statistically significantly higher in the 5-FU side than in the control side in all body parts ($p < 0.001$). ○ Good response (51%-75% repigmentation): NB-UVB + intradermal 5FU, 16 patients; NB-UVB alone, two patients. ○ Excellent response (76%-100% repigmentation): NB-UVB + intradermal 5FU, 29 patients; NB-UVB alone, four patients.
Abdel Latif, A. A. (2015). Dermatol Ther 28: 383-389.[92] Within-patient RCT, single centre Egypt Outpatient clinic 3 mos. f/u	N=36 F: 15; M: 21 **Age range, yrs:** 6-64 **Mean duration of vitiligo (SD), yrs:** 6.03 (3.56)	Group A: calcipotriol + betamethasone daily Group B: MEL biweekly sessions Patients were treated for 3 mos.	Forty-four patients were initially recruited; however, eight patients did not complete the 12 wks. study duration for unknown reasons. A total of 72 lesions were included. **Repigmentation:** ○ There was a statistically significant improvement in symptoms in both groups of lesions after 12 wks., but there was no statistically significant difference between treatments at the end of the study. **Side effects:** ○ Erythema was observed in five patients (13.8%) in group A versus nine patients (25%) in group B. Five patients (13.8%) showed hyperpigmentation in the surrounding normal skin in the side treated by excimer light.

Study details	Population	Intervention & Comparator	Comments
Abdel Sabour Makki, M., W. Saudi, et al. (2019). Journal of the Egyptian Women's Dermatologic Society 16(3): 179-183.[116] Non-randomized within-patient comparative study, single centre Egypt Hospital 3 mos. f/u	N=22 F: 13; M: 9 **Mean age, yrs.:** 23.5 (2.6) **Mean (SD) duration of vitiligo, yrs.:** 6.09 (1.49)	Group A (n=22 patches): carbon dioxide laser-assisted dermabrasion + topical 5-FU applied daily for 2 wks. + twice weekly excimer light sessions Group B (n=22 patches): mechanical dermabrasion + topical 5-FU applied daily for 2 wks. + twice weekly excimer light sessions	**Repigmentation (> 75%)** Group A, 6/22; Group B, 9/22 **Repigmentation (50 – 75%)** Group A, 10/22; Group B, 9/22 **Adverse effects:** Group A, hyperpigmentation (2/22) and scarring (single patch); Group B, hyperpigmentation (11/22) and scarring (6/22)
Bae, J. M. (2019). Lasers in surgery and medicine 51: 239-244.[117] Within-patient RCT, single centre Korea Hospital 12 wks. f/u	N=21 F: 14; M: 7 **Median (range), yr.:** 49 (21 – 79) **Median (range) duration of vitiligo, mo.:** 18 (1 – 240)	Group A (n=37 patches): 311-nm Titanium: Sapphire Laser twice wkly. Group B (n=37 patches): 308-nm excimer laser twice wkly. Treatment for 12 wks.	**Attrition:** 5/21 (24%) due to irregular working hours **Repigmentation 76 – 100%** Group A, 14/37 (37.8%); Group B, 12/37 (32.4%) **Adverse effects:** Persistent erythema (> 48 hrs.)

Study details	Population	Intervention & Comparator	Comments
Cherif, F. (2003). Dermatol Online J 9:4.[93] Within-patient non-randomized, single centre Tunisia Hospital 15 wks. f/u	N=23 F: 16; M: 7 **Mean age (range), yrs:** 36(19-73) **Mean duration (range), yrs:** 11(1-31)	Group A: calcipotriol (0.005%) twice daily + PUVA three times weekly Group B: PUVA three times weekly Patients were treated for 15 wks.	**Repigmentation:** **Marked response (>50%)** Group A, 12 patients Group B, 7 patients
Dayal, S. (2016). Pediatrdermatol33: 646-651.[103] Within-patient *non-randomized* single centre study India University setting 6 mos.	N=20 (children) F: 11; M: 9 **Mean (SD) [range] age, yrs.:** 11.1 (2.9) [5-14] **Mean (SD) [range] duration of vitiligo, yrs.:** 3.2 (3.1) [1 mo. – 10 yrs.)	Group A: tacrolimus 0.03% ointment twice daily + NB-UVB three times a wk. Group B: NB-UVB three times a wk. The irradiation dose was increased by 20% on each subsequent visit. Patients were treated for 6 mos.	**Excellent response (>75%) according to lesion site:** Face: group A, 5; group B, 2 Trunk: group A, 1; group B, 0 Proximal limbs: group A, 2; group B, 0 **Good response (51-75% repigmentation) according to lesion site:** Face: group A, 0; group B, 1 Trunk: group A, 2; group B, 0 Proximal limbs: group A, 2; group B, 1 The number of treatment sessions and the mean cumulative dosage required for the induction of the first clinically visible response was significantly less for group A compared with group B ($p < 0.05$).

Study details	Population	Intervention & Comparator	Comments
Doghaim, N. N. (2019). Journal of Cosmetic Dermatology 18: 142-149.[118] Within-patient RCT, single centre Egypt Outpatient clinic 3 mos. f/u	N=32 F: 24; M: 8 **Mean (SD) [range] age, yrs.:** 28 (5.65) [18 – 35] **Mean (SD) [range] duration of vitiligo, yrs.:** 2.72 (1.03) [1 – 5]	Group A: Fractional CO_2 laser 2 mos. apart + NB-UVB twice weekly for 2 mos. (in between the two sessions of CO_2) Group B: NB-UVB thrice weekly Treatment for 4 mos.	**Repigmentation >75% (≥ 75%):** Group A, 8/32 (25%); Group B, 0/32 (0%) **Repigmentation >50% (50 – 75%):** Group A, 2/32 (6%); Group B, 2/32 (6%)
Doghaim, N. N., R. A. El-Tatawy, et al. (2020). J Cosmet Dermatol 19(1): 122-130.[119] Within-patient non-randomized comparative, single centre Egypt Outpatient clinic 3 mos. f/u	N=40 F: 32; M: 8 **Mean (SD) [range] age, yrs.:** 20.25 (14.10) [12 – 60] **Mean (SD) [range] duration of vitiligo, yrs.:** 4.80 (4.54) [1 – 20]	Group A: laser (Nd:Yag laser + NB-UVB) Group B: NB-UVB Treatment for 4 mos.	**Repigmentation >75% - 100%** Group A, 12/40 (30%); Group B, 0/40 (0%) **Repigmentation >50% - 75%** Group A, 15/40 (37.5%); Group B, 4/40 (10%) **Patient satisfaction rate, very satisfied (>75% satisfaction rate):** Group A, 10/40 (25%); Group B, 4/40 (4%)

Study details	Population	Intervention & Comparator	Comments
Eldelee, S. A., S. F. Gheida, et al. (2019). J Dermatolog Treat: 1-8. (accepted manuscript)[120] Within-patient non-randomized comparative, single centre Egypt Outpatient clinic 3 mos. f/u	N=27 F: 16; M:11 **Mean (SD) [range] age, yrs.:** 29.93 (15.32) [11 – 55] **Mean (range) duration of vitiligo, yrs.:** 2.67 (1.66) [1 – 9]	Group A (27 patches): NB-UVB twice per week + prostaglandin F2 alpha Group B (27 patches): NB-UVB twice per week Treatment for a maximum of 3 mos.	**Repigmentation 76 – 99%** Group A, 6/27 (22%); Group B, 0/27 (0%) **Repigmentation 51 – 75%** Group A, 9/27 (33%); Group B, 0/27 (0%) **Side effects:** Group A, NR; Group B, erythema (2/27); pain during injection (5/27)
Esme, P., G. Gur Aksoy, et al. (2019). Dermatol Surg 45(12): 1627-1634.[121] Within-patient RCT, single centre Egypt Outpatient clinic 4 wk. post-treatment f/u	N=30 F: 19; M: 11 **Mean (SD) [range] age, yrs.:** 38.50 (12.31) [18 – 60] **Mean (SD) [range] duration of vitiligo, yrs.:** 10.41 (7.73) [2 – 31]	Group A (51 patches): Ablative CO_2 laser applied with 2 weekly intervals for 7 sessions. Group B (51 patches): NB-UVB thrice weekly Treatment for 4 mos.	**Repigmentation > 75% - 100%** Group A, not reported; Group B, 1/51 **Adverse effects:** No serious adverse effects were observed. Koebner phenomenon, 6/51

Study details	Population	Intervention & Comparator	Comments
Ghasemloo, S. (2019). J Dermatolog Treat 30: 697-700.[122] Within-patient RCT, single centre Iran Hospital 16- wk. f/u	N=30 F: 13; M: 17 **Mean age (SD), yrs.:** 42.6 (15.1) **Mean duration of vitiligo, yrs.:** 10.03 (7.98)	Group A: CO_2 + NB-UVB Group B: NB-UVB monotherapy Treatment for 16 wks.	**Repigmentation >75%** Group A, 2/30 (7%); Group B, 0/30 (0%) **Repigmentation 51 – 75%** Group A, 2/30 (7%); Group B, 0/30 (0%) Overall repigmentation was greater in group A compared with group B (p = 0.002)

Study details	Population	Intervention & Comparator	Comments
Goktas, E. O. (2006). J Eur Acad Dermatol Venereol 20: 553-557.[94] Within-patient non-randomized single centre Turkey University setting 6 mos. f/u	N=28 F: 13; M: 11 **Mean age (range), yrs:** 34.2 (16-53) **Mean duration (SD) [range], yrs:** 9.4 (6.9) [1-22]	Group A: Calcipotriol twice daily + NB-UVB (right side) Group B: NB-UVB (left side) Patients were treated for 6 mos.	Attrition: four out of the 28 patients did not complete the study due to personal reasons. **Repigmentation by lesion site:** **>50% repigmentation in Group A** Trunk, 9 patients Upper extremities, 5 patients Lower extremities, 6 patients Hands, none Feet, none **>50% repigmentation in Group B** Trunk, 5 patients Upper extremities, 4 patients Lower extremities, 3 patients Hands, none Feet, none **>75% repigmentation in Group A** Trunk, 4 patients Upper extremities, 4 patients Lower extremities, 3 patients Hands, none Feet, none **>75% repigmentation in Group B** Trunk, 5 patients Upper extremities, 1 patient Lower extremities, 3 patients Hands, none Feet, none

Study details	Population	Intervention & Comparator	Comments
Ibrahim, Z. A. (2016). J Cosmet Dermatol 15: 108-116.[95] Within-patient non-randomized, single centre Egypt Outpatient clinic 3 mos. after the last session	N=60 F: 34; M: 26 **Mean age (SD) [range], yrs:** 28 (5.65) [18-35] **Mean age of onset of disease (SD) [range], yrs:** 5.9 (6.2) [1-10]	Group A: NB-UVB + intradermal injection of PRP Group B: NB-UVB alone Patients were treated for 4 mos.	**Repigmentation:** **Good response (>50% to 75%)** Group A, 12 patients **Excellent response (>75% to 100%):** Group A, 33 patients In the control group there were no patients who had excellent or good response. **Side effects:** Thirty three of the 60 patients reported some side effects: pain during injection in 30 patients (50%); ecchymosis (Discolouration of the skin due to bruising) in nine patients (15%).
Kadry, M. (2018). Clinical, cosmetic and investigational dermatology 11: 551-559.[123] Within-patient RCT, single centre Egypt University setting 12 wks. f/u	N=30 F: 22; M: 18 **Mean (SD) age, yrs.:** 32.03 (12.29) **Median (range) duration of vitiligo, mos.:** 12 (6 – 120)	Group A: Fractional CO_2 laser + PRP Group B: CO_2 *N.B. other interventions investigated in this study are presented in table 25*	**Repigmentation:** Not reported in a way that meets protocol requirements. **Side effects:** Group A, pain (23.33%), hyperpigmentation (6.66%); Group B, pain (26.6%) Inflammation was experienced in both groups.

Study details	Population	Intervention & Comparator	Comments
Khullar, G. (2015). J Eur Acad Dermatol Venereol 29: 925-932.[109] Within-patient RCT, single centre India Hospital 6 mos. f/u	N=25 F: 5; M: 20 **Mean age (SD) [range]:** 24.4 (8.6) [12-37] **Mean duration of vitiligo (SD) [range], yrs:** 9.7 (4.9) [2-20]	Group A: Topical calcipotriol (0.005%) + NB-UVB Group B: NB-UVB Patients were treated for 6 mos.	Attrition: two patients withdrew from the study. **Repigmentation:** ○ The percentage repigmentation of target lesions was greater in group B compared with group A, but the difference was not statistically significant. ○ Mean (SD) [95% CI] percentage decrease in Lund & Bowder score to estimate the total body surface area affected (percentage repigmentation) at 24 wks.: Group A, 49.0 (24.5) [38.9-59.1]; Group B, 51.4 (28.1) [39.8-60.3] ○ The authors concluded that the addition of calcipotriol to NB-UVB probably does not enhance the extent of repigmentation and the time to initial repigmentation but that larger randomized placebo-controlled trials are necessary.
Kullavanijaya, P. (2004). Photodermatol Photoimmunol Photomed 20: 248-251.[285] Within-patient, non-randomized USA Hospital setting	N=17 F: 6; M: 11 **Mean age (range), yrs.:** 44.6 years (17–68) **Mean (range) duration of vitiligo, yrs:** 7.3 (0.8 – 20)	Group A: NB-UVB + calcipotriene (applied after NB-UVB exposure) Group B: NB-UVB three times a week	Overall, 20 patients were enrolled, three patients did not follow instructions for the application of calcipotriene; the response of these patients was not included in the analysis. One patient was not exposed to NB-UVB. **Significant repigmentation (66-100%):** 8/17 (47%) **Moderate repigmentation (26-65%):** 6/17 (35%)

Study details	Population	Intervention & Comparator	Comments
15 mos. f/u			Nine of 17 patients had better improvement on the NB-UVB and calcipotriene side by 29–114 treatments No new lesions occurred during the treatment period. **Adverse effects:** All patients tolerated the combination treatment well, no adverse effects were detected.
Orecchia, G. (1992). Dermatology 184: 120-123.[96] Within-patient, non-randomized, single centre study Italy University setting 4 mos. f/u	N=41 F: 23; M: 18 **Mean age (range), yrs:** 31 (18-54) **Mean (range) duration of vitiligo, yrs:** 7 (2-25)	• All patients received Khellin 2% + sunlight on one side • Of the 41 patients, 36 patients also received placebo (acetone + propylene glycol) + sunlight on the other side • The remaining five patients did not receive any treatment on the other side The duration of sunlight exposure was adapted to the skin type and to the tolerance of the patients. The duration gradually increased from the first exposure of 10 min to a maximum of 90 min. The therapy consisted of three exposures/week. Patients were treated for 4 mos.	**Repigmentation >50%, n (%):** ○ Khellin 2% + sunlight, 10 (24.3) ○ Placebo + sunlight, 8 (22.3) ○ Untreated, 0 (0) **Repigmentation >75%, n (%):** ○ Khellin 2% + sunlight, 0 (0) ○ Placebo + sunlight, 0 (0) ○ Untreated, 0 (0)
Orecchia, G. (1998) J Dermatolog Treat, 9: 65-9[97] Within patient, non-randomized, single centre study Italy	N=36 F: 22; M: 14 **Mean age (range), yrs:** 28.1 (9-60) **Mean duration of vitiligo (range), yrs:** (6 mos.-32 yrs.)	Group A: Khellin + water/2-propanol/propylene1% Glycol + UVA Group B: Placebo + UVA Patients were treated for 6 mos.	<u>Dichotomous outcomes with no/insufficient raw data provided:</u> **Repigmentation:** ○ Of the 36 patients, 31 patients (86.1%) showed a favourable response (> 11% repigmentation). Of the 31 patients, 11 (35.5%) had an excellent response (≥ 51% repigmentation).

Study details	Population	Intervention & Comparator	Comments
University setting 6 mos.			**Repigmentation ≥50% (>50%) at 6 mos.** RR = 5.5 SE = 0.707 P = 0.0159
Park, M. J., U. Shon, et al. (2019). Photodermatol Photoimmunol Photomed. 00: 1 -8[124] Within-patient RCT, single centre Korea University setting 12 wks. f/u	N=10 (13 pairs) F: 3; M: 7 **Mean age, yrs.:** 50.2 **Mean (range) duration of vitiligo, mos.:** 7.6 (1 – 24)	Group A (13 patches): 308 nm excimer laser twice weekly Group B (13 patches): 311-nm titanium:sapphire lasers (TSL) twice weekly Treatment for 12 weeks.	**Mean (SD) repigmentation rate** Overall: Group A, 49.99% (20.99); Group B, 52.82% (19.89) **Disease-stable sub-group:** Group A, 55.5% (26.74%); Group B, 55% (20.81%) **Patient satisfaction:** Group A, 2.80 (moderate improvement); Group B, 2.0 (moderate improvement) **Adverse effects:** There was no serious adverse effect requiring cessation of treatments. **Mean (SD) persistent erythema severity score:** Group A, 2.38 (1.94); Group B, 0.77 (0.93), p = 0.029
Sahu, P. (2016). Photodermatol Photoimmunol Photomed 32: 262-268.[104] Within-patient *non-randomized* comparative study India	N=30 F: 19; M: 11 **Mean (SD) [range] age, yrs.:** 31.63 (9.069) [20-57] **Mean (SD) [range] duration of vitiligo, yrs.:** 8.63 (4.789) [2-19]	Group A: tacalcitol ointment OD + NB-UVB thrice weekly Group B: NB-UVB thrice weekly Patients were treated for 24 wks.	**Excellent repigmentation (75 – 100%)** Group A, 30%; group B, 0 **Good repigmentation (50 – 74%)** Group A, 53.33%; group B, 43.33% **Side effects:** Most patients had no side effects; Side effects included erythema, blistering, and pruritus.

Study details	Population	Intervention & Comparator	Comments
University setting 24 wks.			Combination therapy was associated with more side effects than monotherapy (p > 0.05)
Sharma, S. (2018). J Eur Acad Dermatol Venereol 32: e330 - 1.[105] Within-patient RCT India University setting 24 wks. f/u	N=25 F: NR; M: NR **Age:** NR **Duration of vitiligo:** NR	Group A: NB-UVB + topical bimatoprost 0.03% eye drops Group B: NB-UVB Patients were treated for 24 wks.	Repigmentation >50% was achieved in 13 (52%) patients in group A and 10 (40%) patients in group B, difference was not statistically significant.
Soliman, M. (2016). J Cosmet Laser Ther 18: 7-11.[108] Within-patient RCT Egypt University setting 6 mos. f/u	N=30 F: 18; M: 12 **Mean (SD) [range] age, yrs.:** 22.27 (14.22) [4-64] **Mean (SD) [range] duration of vitiligo, yrs.:** 5.14 (2.28) [0.25-9.0]	Group A: topical antioxidant OD + excimer light twice weekly Group B: excimer light twice weekly A maximum of 24 excimer light sessions were given. Treatment lasted 3 mos.	**Repigmentation:** Repigmentation >75% was achieved in 9 (22%) of group A lesions and in 0 (0%) of group B lesions. **Patient satisfaction, cosmetic acceptability:** Excellent: group A, n =9; group B, n =0 Good: group A, n = 8; group B, n = 0 Moderate: group A, n = 7; group B, n = 19 Poor: group A, n = 6; group B, n = 11

Abbreviations: 5FU, fluorouracil; CO_2 carbon dioxide; F, female; hr., hour; M, male; MEL, monochromatic excimer light; mos. months; NA, not applicable; NB-UVB, narrow band UVB; PRP, platelet-rich plasma; RR, risk ratio; SE, standard error; SD, standard deviation; TSL, titanium sapphire lasers; UVA, ultraviolet A; UVB, ultraviolet B; wks., weeks; yrs., years.

Table 24: Summary of within-patient studies investigating surgical therapies

Study details	Population	Intervention & Comparator	Comments
Attwa, E. M., S. A. Khashaba, et al. (2020). J Cosmet Dermatol 19: 1473 - 1478 [111] Non-randomized within-patient comparative study, single-centre Egypt Outpatient clinic 3 mos. f/u	N=27 F: 12; M: 15 **Mean age (SD), yrs.:** 26.7 (17.5) **Median duration:**75.4 ± 10.0 mos.	Group A (27 patches): microneedling + 5-FU once every two weeks, the session was repeated every 15 days for 3 mos. Group B (27 patches): microneedling Chosen site was anesthetized with lidocaine cream. Treatment for 3 mos.	**50 – 75% repigmentation:** Group A, 1 (3.7%); Group B, 0 (0%) **> 75% repigmentation:** Group A, 1 (3.7%); Group B, 0 (0%) **Side effects:** Group A: pain (n = 6), itching (n = 3), pain and itching (n = 5); Group B: pain (n = 13) (p = 0.013)
Bao, H. (2015). J Dermatolog Treat 26: 571-574.[98] Within patient, non-randomized, single centre, comparative study China Clinic 12 mos. f/u	N=83 F: 45; M: 38 **Mean age (SD), yrs:** 25.2 (10.5) **Duration of vitiligo:** NR	Group A: Blister roof grafting (BG) Group B: Cultured melanocytes transplantation (CMT) Group C: Non-cultured epidermal cell suspension transplantation (NCES)	**Repigmentation:** ○ Excellent repigmentation (≥90 %) was observed in 76%, 55%, and 53% of patients treated with the BG, CMT, and NCES methods, respectively. Statistically significant differences were observed between the BG and CMT methods (p=0.038), and the BG and NCES methods (p=0.017). But no statistically significant difference was observed between the CMT and NCES methods (p= 0.986). ○ The extent of repigmentation in the head, neck, and trunk was better than that in the extremities with all three transplantation methods. **Adverse effects:** ○ None of the patients developed infection, milia or visible scarring at any donor or recipient site.

Study details	Population	Intervention & Comparator	Comments
Donaparthi, N. (2016). Indian Jof Dermatol 61: 640-644.[128] Within-patient, non-randomized, single centre, comparative study India Outpatient 24 wks. f/u	N=11; 60 patches were treated. F: 6; M: 5 **Mean age (SD), yrs.:** group A, 18.00 (3.52); group B, 31.40 (12.46) **Mean (SD) duration of disease, yrs.:** group A, 12.13(4.31); group B, 25.40(8.85)	Group A: epidermal melanocyte transfer (EMT) Group B: hair follicular melanocyte transfer (HFMT)	**Repigmentation >75%:** Group A, 90%; Group B, 43.34%, $p < 0.05$
Ebadi, A. (2015) J Eur Acad Dermatol Venereol 29: 745-51.[99] Within-patient, non-randomized comparative study Iran Hospital 2 wks. f/u	N=10; 39 patches were treated. F: 6; M: 4 **Mean (median) [SD] age, yrs**: 31.8 (30.5) [8.9] **Median duration (range) of disease, yrs:** 4.5 (3-17)	Group A: MKT alone Group B: MKT + excimer laser Group C: Excimer laser alone Group D: Control (no treatment) Dermabrasion was conducted manually on all patches. Overall 39 patches were treated: MKT alone, nine patches; MKT + excimer laser, 10 patches; excimer alone, 10; patches without any treatment (control), 10 patches	Attrition: In this study, 16 patients were initially included but 6 of them were excluded (five had organ specific antibody, one patient withdrew from the study due to a car accident after four sessions of laser therapy. **Repigmentation ≥50% (≥65%):** Group A,1 patch; Group B, 4 patches; Group C, 0 patches; Group D, 0 patches. **Repigmentation ≥75% (≥95%):** Group A, 0 patches; Group B, 2 patches; Group C,0 patches; Group D,0 patches

Study details	Population	Intervention & Comparator	Comments
Komen, L. (2017).J Dermatol Treat 28: 86-91.[106] Within-patient RCT The Netherlands Medical centre 6 mos. f/u	N=33 patients (42 pairs of lesions) F = 13; M = 20 **Mean (median) [range] age, yrs.:** 35.8 (36) [18-61] **Duration of vitiligo (n =18):** 1-5 years, 9%; 5-10 years, 0%; >10 years, 91%	Group A: 1.5mm deep punch grafts Group B: 1.5mm superficial punch grafts Group C: 1.0mm deep punch grafts Group D: 1.0 mm superficial punch grafts Four depigmented lesions in each patient were randomly allocated to receive four punch grafts/lesion/ Matched punch grafts of the donor site localised on the hip were taken and directly placed on into the prepared recipient site. Five days after the transplantation, UV treatment was started at home, twice weekly, and continued until 3 mos. after the procedure.	**Patient Global Assessment, n (%) for donor sites (n=28)** **Group A:** Poor, 1 (3.6) Neutral, 5 (17.9) Good, 10 (35.7) Very good,12 (42.9) **Group B:** Poor, none Neutral, 4(14.3) Good, 11(39.3) Very good, 13(46.4) **Group C:** Poor, none Neutral, 3(10.7) Good, 13(46.4) Very good, 12(42.9) **Group D:** Poor, none Neutral, 2(7.1) Good, 14(50) Very good, 12(42.9) **Patient global assessment, n (%) for recipient sites (n=25)** **Group A:** Very poor, 3(12) Poor, 2(8) Neutral 1 (4) Good 12 (48) Very good 7 (28)

Study details	Population	Intervention & Comparator	Comments
			Group B: Very poor, 3 (12) Poor, 1 (4) Neutral, 4 (16) Good, 12 (48) Very good, 5 (20) **Group C:** Very poor, 3 (12) Poor, 2 (8) Neutral, 2 (8) Good, 14 (56) Very good, 4 (16) **Group D:** Very poor, 3 (12) Poor, 3 (12) Neutral, 3 (12) Good, 12 (48) Very good, 4 (16) **Side effects:** For the donor site, group A showed more hypopigmentation compared with group D ($p = 0.01$) and more erythema compared with group B, group C, and group D ($p< 0.01$; $p=0.01$; $p<0.01$ respectively) For the donor site, group A showed more cobblestone formation compared with group D ($p = 0.03$). Group B showed more cobblestone formation compared with group D ($p =0.05$). The physicians experienced that the 1.5mm superficial grafts were easier to harvest and to transplant than the 1.0mm and deep grafts.

Study details	Population	Intervention & Comparator	Comments
Mrigpuri, S. (2019). Journal of the European Academy of Dermatology and Venereology: JEADV 33: 185-190.[112] Within-patient RCT, single-centre India Hospital setting (tertiary centre) 16 wks. f/u	N=30 F: 16; M: 14 **Mean (SD) [range], yrs.:** 24.23 (5.81) [13 – 36] **Median (IQR) duration of vitiligo, yrs.:** 8 (6 – 13)	Group A (41 patches): NCES 4 compartment method Group B (41 patches): lab-NCES	**Repigmentation (≥ 75%)** Group A, 68%; Group B, 71% **Repigmentation (≥ 90%)** Group A, 34%; Group B, 37%
Muhammed, R. T. (2018). JAMA dermatology 154: 301-308.[113] Within-patient RCT, single centre India Tertiary care centre 16 wk. f/u	N=30 F: 18; M: 12 **Mean (SD) age, yrs.:** 23.37 (6.43) **Median (range) duration of vitiligo, yrs.:** 8 (5-13)	Group A (42 patches): ECS + FCS transplantation Group B (42 patches): ECS transplantation	**Repigmentation ≥75%** Group A, 32/42 (76%); Group B, 24/42 (57%) **Repigmentation ≥90%** Group A, 22/42 (52%); Group B, 13/42 (31%)

Study details	Population	Intervention & Comparator	Comments
Parambath, N. (2019). International Journal of Dermatology 58: 472-476.[114] Within-patient RCT, single-centre India Tertiary Care Centre 6 mos. f/u	N=21 F: 13; M: 8 **Mean (SD) age, yrs.:** 23.1 (7.6) [21 – 25] **Mean duration of vitiligo, yrs.:** 4.5	Group A (n=21 patches): NCES suspended in PRP Group B (n=21 patches): NCES suspended in PBS	**Repigmentation ≥75% (> 75%)** Group A, 16/21; Group B, 11/21 **Repigmentation >90%** Group A, 9/21; Group B, 5/21 **Mean (SD) patient satisfaction using visual analogue scale:** Group A, 72% (30); Group B, 58% (32) (p = 0.001)
Razmi, T. M. (2018). JAMA Dermatol 154: 301-308.[107] Within-patient RCT India Hospital 16 wks. f/u	N=30 F=18; M=12 **Mean (SD) age, yrs.:** 23.37 (6.43) **Duration of vitiligo, median (IQR), yrs.:** 8 (5-13)	Group A: Epidermal Cell Suspension (ECS) + Follicular Cell Suspension (FCS) Group B: ECS Dermabrasion was conducted manually under local anaesthesia until pinpoint bleeding was noted.	**Repigmentation ≥75%, n (%):** Group A, 32/42(76); Group B, 24/42(57), p< 0.001 **N.B. Repigmentation ≥90%, n (%):** Group A, 22/42(52); Group B, 13/42(31), p = 0.001
Tawfik, Y. M. (2019). Journal of Cosmetic	N=42 F: 29; M: 13	Group A1 (n=25 patches): melanocyte and keratinocyte transplantation (MKTP) using a donor-to-recipient (D/R) of 1/3	**Repigmentation 90% - 100%** Group A, 15/25 (60%); Group A2, 16/25 (64%); Group B1, 1/26 (3.8%); Group B2, 1/26 (3.8%)

Study details	Population	Intervention & Comparator	Comments
Dermatology 18: 638-646.[115] Within-patient RCT, multicentre Egypt Outpatient clinic 6 mos. f/u	**Mean (SD) age, yrs.:** Group A, 24.29 (6.63); Group B, 22.86 (7.74) **Mean duration of vitiligo, yrs.:** Group A, 8.67 (2.52); Group B, 8.57 (3.59)	Group A2 (n=25 patches): MKTP using a D/R of 1/3 + NB-UVB Group B1 (n=26 patches): MKTP using D/R of 1/10 Group B2 (n=26 patches): MKTP using D/R of 1/10 + NB-UVB Treatment for 6 mos.	**Repigmentation 75% - 89%** Group A1, 5/25 (20%); Group A2 6/25 (24%); Group B1, 1/26 (3.8%); Group B2, 2/26 (7.7%)

Abbreviations: BG, blister roof grafting, CMT, cultured melanocytes transplantation; ECS, epidermal cell suspension; F, female; FCS, follicular cell suspension; IQR, interquartile range; lab-NCES, laboratory non-cultured epidermal suspension; M, male; MKT, melanocytes-keratinocytes transplantation; MKTP, melanocyte and keratinocyte transplantation procedure; NA, not applicable; NCES, non-cultured epidermal cell suspension transplantation; NR, not reported; PBS, phosphate buffered saline; PRP, platelet rich plasma; SD, standard deviation; yrs., years.

Table 25: Summary of within-patient studies investigating complementary therapies

Study details	Population	Intervention & Comparator	Comments
Kadry, M. (2018). Clinical, cosmetic and investigational dermatology 11: 551-559.[123] Within-patient RCT, single centre Egypt University setting 12 wks. f/u	N=30 F: 22; M: 18 **Mean (SD) age, yrs.:** 32.03 (12.29) **Median (range) duration of vitiligo, mos.:** 12 (6 – 120)	Group A: Fractional CO_2 laser + PRP Group B: PRP *N.B. other interventions investigated in this study are presented in table 23*	**Repigmentation:** Not reported in a way that meets protocol requirements. **Side effects:** Group A, pain (23.33%), hyperpigmentation (6.66%); Group B, pain (33.3%) Inflammation was experienced in both groups.

Table 26: Summary of non-comparative studies investigating topical therapies

Study details	Study population	Intervention	Notes
Joshipura, MD (2018) J Am Acad Dermatol[130] Case series (prospective), 32 wk. extension study of Rothstein, BA (2017) J Am Acad Dermatol 76: 1054-1060.	N=8*	Ruxolitinib 1.5% cream twice daily + optional NB-UVB	*8/9 of patients who completed the 20 wks. study continued to the extension study. Attrition: 3 patients did not complete the 32-wk. extension study due to a lack of response (but included in analysis). Three patients opted for NB-UVB (twice weekly), a statistically significant mean improvement in overall VASI of mean (SD), 37.6% (31.2%) (p=0.011). In patients with >0.5% facial surface area affected (N=4), a statistically significant mean improvement of mean (SD), 92% (7.1%) (p=0.0001) VASI at wk. 52 with one patient being completely repigmented. There was a statistically significant mean improvement in the overall VASI score at wk. 52, this was most pronounced for those treated for facial vitiligo.
Rokni, G. R. (2017). J Adv Pharm Technol Res 8: 29-33.[143] Iran Prospective case series Hospital setting 24 wks. f/u	N=30 F: 18; M: 12 **Mean (SD) [range] age, yrs.:** 26.13 (18.20) [2 – 76] **Mean (SD) duration of vitiligo, yrs.:** 3.77 (0.74)	1% tacrolimus applied twice daily	**Excellent repigmentation (76 – 100%), %:** Head and neck: 32 Body: 14.3 Upper limb: 8.3 Lower limb: 11.1 Genital: 0 **Moderate repigmentation (51 – 75%), %:** Head and neck: 60 Body: 21.4 Upper limb: 16.7 Lower limb: 11.1 Genital: 33.3 *N.B. authors reported repigmentation at 4, 8, 12,16, and 20 weeks but only 24-week data is reported here.*

Study details	Study population	Intervention	Notes
Rothstein, BA (2017) J Am Acad Dermatol 76: 1054-1060.[129] Case series (prospective) USA Outpatient 20 wks. f/u	N=12 F: 5; M: 6 **Mean age (range), yrs.:** 52 (33-65) **Mean duration of vitiligo (range), yrs.:** 8.45 (3-18)	Ruxolitinib 1.5% cream twice daily Application was limited to 10% BSA exposure or maximum 3.75g/application to minimise systemic exposure	**Attrition:** 3 patients did not complete the 20 wks. of the study,1 patient did not complete the required laboratory testing;1 patient dropped out of the study after 16 wks. due to a lack of response; 1 patient was lost to follow-up. Eight of the 11 patients had some treatment response, the most significant response consisted of facial repigmentation; four patients showed a statistically significant improvement in VASI scoring of 76%[6] (p = 0.001) at follow-up. Non-facial vitiligo showed minor, non-statistically significant clinical improvement. **QoL:** no statistically significant differences in DLQI were observed at wk. 20 from baseline, but the authors suggest that this is due to the study not being powered enough to detect any change. Adverse effects: Erythema, rim of hyperpigmentation surrounding the vitiligo patches was observed on facial and acral parches in 9 of 11 patients.
Shashikiran, A. R. (2018). Indian J Dermatol Venereol Leprol 84: 203-205.[144] India Prospective case series Hospital setting 6 mos. f/u	N=39 F: 25; M: 14 **Age range, yrs.:** 13 – 44 **Duration of vitiligo, (range) yrs.:** 1.2 – 11.5	5% fluorouracil needling once a mo. for 3 consecutive mos. 5% fluorouracil and antibiotic cream was applied on the treated area and dressed; patients were asked to apply this twice daily for 15 days	**Repigmentation:** 50-75% repigmentation was seen in 26% of patches Rate of pigmentation was rapid in approximately 8% of the patches, which developed 100% repigmentation within the first mo. Among the responders, cosmetic matching of the repigmentation area was excellent (87%)

Abbreviation: BSA, body surface area; DLQI, dermatology life quality index; F, female; M, male; NB-UVB, narrow band ultraviolet B; QoL, quality of life; SD, standard deviation; SD, standard deviation; VASI, vitiligo area scoring index; wk.; week; yrs., years.

[6] A 50% improvement in VASI score is a clinically successful treatment response.

Appendix H: Narrative findings from non-comparative studies

Table 27: Summary of non-comparative studies investigating depigmentation therapies

Study details	Study population	Intervention	Notes
Boukari, F. (2014) J Eur Acad Dermatol Venereol 28: 374-7.[131] Case series (retrospective) France Hospital Mean follow-up: 36 mos.	N=6 F: 6; M: 0 **Mean age (range), yrs.:** 60.67 (51-79) **Mean (range) duration of vitiligo, yrs.:** 19.33 (8-31)	Laser assisted depigmentation (QS laser) Patients were treated for a median (range) of 3 (1-20) sessions; one patient was treated for 20 sessions	**Depigmentation:** • Complete depigmentation was achieved in all patients. • A median (range) of 2 (1-6) sessions were necessary for achieving complete depigmentation **Relapse (repigmentation):** • A complete repigmentation was observed after 21 mos. in one patient • 50% repigmentation was noted in one patient 7 mos. after the end of treatment • Two patients showed minimal repigmentation (<25%), 18 mos. and 9 yrs.
Komen, L. (2013) Br J Dermatol 169: 1246-51.[132] Case series (retrospective) The Netherlands Hospital Mean follow-up: 13 mos.	N=27 F: 15; M: 12 **Mean age (median; range), yrs.:** 50 (53; 10-89) **Mean (median; range) duration of vitiligo, yrs.:** 25 (21; 4-58)	694-nm QSR laser Treatment took place every 6-8 wks. until the entire pigmented area was treated.	**Attrition:** Of the 48 patients who were treated with QSR laser, only 27 (56%) participated in the study. This was due to patients not responding to invitations or refusing to participate. **Depigmentation:** >75% depigmentation was achieved in 13 patients <75% depigmentation was achieved in 14 patients The results for patients with active disease were significantly better than those of patients with stable disease (p = 0.046) The mean number of treatments/areas was three for patients with >75 depigmentation and eight for patients with <75% depigmentation after treatment. **Side effects:** Eighteen patients (67%) reported one or more side effects. These side effects were erythema, crusting, itch and bullae but all of these were temporary. One patient did not complete laser treatment due to the pain related to the treatment.
Majid, I. (2013) J Cutan Aesthet Surg 6: 93-6.[133] Case series (prospective)	N=15 F: 11; M: 4 **Mean age (range), yrs:** 27 (15-42)	Q-switched Nd: YAG laser at 532-nm wavelength.	All 15 patients were treated on the face; 6 treated on the hands; 3 treated on the forearms; 2 treated on the feet Patients were called for follow-up at 1st, 2nd and 6 wks.

Study details	Study population	Intervention	Notes
India University 6 wks. f/u	**Mean (range) duration of vitiligo, yrs**: 10.6 (2-25)	All 15 patients had not responded satisfactorily to topical application of MBEH for at least 3 mos.; before each treatment topical treatment with MBEH was discontinued. MBEH was continued at bedtime along with the laser sessions on all treated areas. In all enrolled patients only one area of the body was treated in a single session.	**Depigmentation:** • Most patients responded well to the treatment with >90% resolution of pigment seen in 13 of 15 patients enrolled. • Only 2 patients had a poor response with <50% resolution of pigment. **Relapse:** At 3-mo. follow-up no patients experienced relapse.
Majid, I. (2017). Lasers Med Sci 32: 851-855.[145] India Retrospective case series Hospital 2-5 yrs. (2.78 yrs. average)	N=28 F: 17; M: 11 **Mean (range) age, yrs.:** 28.9 (14-52) **Duration of vitiligo:** NR	532-nm QS Nd: YAG laser treatment Topical steroid-antibiotic combination cream was used on the treated area for 2-3 days after each laser session. Broad-spectrum sunscreen every 4-6 hrs.	A satisfactory treatment response (>90% resolution of pigmentation) was documented in 89.3% of cases (25/28) A poor response (<50% resolution of pigment) was documented in 10.7% of cases (3/28) Relapse was reported in 7/25 of cases MBEH was used by 11/25 responders in the follow-up period to maintain the therapeutic effects of lasers; 14/25 responders were able to maintain therapeutic effects with regular sunscreen use only. **Side effects:** No significant side effects to the laser treatment were reported by any patient and the procedure was termed “tolerable” by all cases.

Study details	Study population	Intervention	Notes
		Treatment sessions were performed at 6- to 8- wk. intervals. Monobenzyl ether of hydroquninone (MBEH)	
Tan, E. S. (2015) Br J Dermatol 172: 1662-4.[134] Case series (retrospective) UK Hospital 5.4 yrs. f/u	N=53 F: 42 M: 11 **Mean (median) [range] age, yrs:** 42.3 (43.0) [10-73] **Mean duration of vitiligo (median) [range], yrs:** 18.5 (15) [2-60]	Monobenzyl ether of hydroquinone (MBEH)	**Depigmentation, n (%):** • Marked but incomplete: 18 (34) • Complete: 31 (58) Although MBEH was so effective at depigmenting the skin, the successfully depigmented skin repigmented after the end of treatment in most patients (38/49, 78%), with sun exposure being the most common trigger (35/38, 92%). **Adverse effects:** • Dose-dependent skin irritation occurred in nearly half of the patients • Rare but more worrying adverse effects were distant depigmentation away from the treated site in one patient, and generalized hypopigmentation in another.
van Geel, N. (2015) J Eur Acad Dermatol Venereol 29: 121-7.[135] Case series (prospective) Belgium Hospital 2 mos. f/u	N=22 F: 17; M: 5 **Mean (median) age, yrs:** 45.27 (46) **Mean (median) age of vitiligo onset:** 26.95 (25.50)	Data collection was obtained from patients who underwent a trial session (test treatment) with cryotherapy and/or 755nm laser therapy on a small area of remaining pigmented skin. Overall, 51 pigmented regions	**Depigmentation:** Overall, there was no significant difference in the capacity to induce depigmentation was observed between cryotherapy (46.7%) and laser therapy (42.9%) after one treatment. The percentage of induced depigmentation after one session was significantly different according to the body location (p= 0.013) with best results on the trunk, followed by the arms, face, neck and less on the hands. In eight test areas without clear response after one session, additional treatments (with an interval of several wks.) were performed on the same test region (cryotherapy in five and laser in three). This resulted in additional depigmentation in all of them, although in one case recurrence of

Study details	Study population	Intervention	Notes
		were exposed to cryotherapy or 755 nm laser therapy.	pigmentation appeared after initial response to laser. The number of additional treatments for cryotherapy ranged from 2 to 4 and for laser from 2 to 3. **Side effects:** Side effects were restricted to cryotherapy and included mild hyperpigmentation, observed in 6/51 test areas and were mainly limited to the face (4/6 test areas).

Abbreviations: BMI, body mass index; CI, confidence interval; F, female; M, male; MBEH, monobenzyl ether of hydroquinone; OR, odds ratio; QS, Q-switched; QSR, Q-switched ruby; SD, standard deviation; UK, United Kingdom; VCD, voluntary cosmetic depigmentation; wks., weeks; yr, year.

Table 28: Summary of non-comparative studies investigating systemic therapies

Study details	Study population	Intervention	Notes
Kim, SR. (2018) JAMA Dermatol 154:370-1.[167] Case study USA Outpatient 3 mos. f/u	N=2 Case 1: female, 30s, 12-year history of vitiligo Case 2: male, 50s, long standing vitiligo	Oral tofacitinib 5mg, twice daily + low dose full-body NB-UVB twice weekly.	Case 1, after 3 mos. of treatment there was nearly complete repigmentation of the face, 75% repigmentation of the neck, chest, forearms, and shins, and only minimal freckling of dorsal hands. Case 2, after 3 mos. of treatment, there was about 50% repigmentation of the face, and, after 6 mos., about 75% facial repigmentation. No repigmentation occurred on other body sites. In contrast to NB UV-B monotherapy, repigmentation using NB UV-B + tofacitinib required relatively low-dose light exposure.
Liu, LY (2017) J Am Acad Dermatol 77: 675-682.e1.[147] Case series (retrospective) USA Outpatient 3 mos. f/u	N=10 F: 5; M: 5 **Age range, yrs.:** 28-55 **Vitiligo duration, yrs.:** 4-33	Oral tofacitinib (some patients had concomitant NB-UVB therapy)	A mean decrease of 5.4% BSA involvement with vitiligo was observed in 5 of 10 patients, whereas the other 5 patients did not achieve any repigmentation. In patients who achieved some repigmentation, it only occurred in sun exposed areas of the skin in 3 patients, diffusely in another patient undergoing concomitant full body NB-UVB phototherapy, and to the dorsal surface of the hands in another patient after initiation of concomitant hand NB-UVB phototherapy. Of the 5 patients who did not experience repigmentation, only 1 patient reported significant sunlight exposure, and the others either avoided sunlight or practiced photoprotection.

Study details	Study population	Intervention	Notes
			The most common adverse effect was upper respiratory infection in 2 patients.
Craiglow, BG. (2015) JAMA Dermatol 151: 1110-2.[148] Case report USA Outpatient 5 mos. f/u	N=1 Female patient in her 50s with widespread and progressive vitiligo for approximately 1 yr.	Oral tofacitinib was initiated at dosage of 5mg every other day, after three wks. the dosage was increased to 5mg/day.	After 2 mos. of therapy, partial repigmentation of the face and upper extremities was evident. After 5 mos., repigmentation of the forehead and hands was nearly complete, and the remaining involved areas demonstrated partial repigmentation. Approximately 5% of the total body surface area remained depigmented. The patient tolerated tofacitinib without adverse effects and there were no abnormalities in the blood results.

Abbreviations: BSA, body surface area; F, female; M, male; NB-UVB, narrow band ultraviolet B; yrs., years.

Table 29: Summary of non-comparative studies investigating combination therapies

Study details	Study population	Intervention	Notes
Fai, D. (2007). J Eur Acad Dermatol Venereol 21: 916-920.[149] Case series (prospective) USA Clinic setting 6 mos. f/u	N=110 F: 42; M: 58 **Mean age (range), yrs:** 42 (18-74) **Duration of vitiligo range:** (1-2 yrs), 26 patients; (3-5 yrs), 51 patients; (>5 yrs), 33 patients.	Concomitant NB-UVB phototherapy was performed twice a week for 16 wks. with once daily application of 0.03% tacrolimus ointment to the affected skin areas of the face, or 0.1% tacrolimus to all lesions located on other sites.	**Degree of repigmentation after 16 wks of treatment:** Repigmentation rate was dependent on the site: an improvement of more than 50% was obtained more frequently for lesions located on the face (73%), limbs (68%) and trunk (53.5%) as compared with lesions located on the extremities (hands and/or feet) and genital areas. **6-mos. post-treatment period in patches previously responding:** Stable response: face, 55%; trunk, 17%; limbs, 11% Relapse: face, 25%; trunk, 30%; limbs, 49% Unknown: face, 20%; trunk, 53%; limbs, 40%
Tsuchiyama, K. (2016). Dermatology 232: 237-241.[150] Case series (prospective) Japan	N=13 F: 10; M: 3 **Age,** ≤16 years **Mean duration of vitiligo (range):** 5.1 years (1-14 yrs.)	Minigraft + phototherapy for approximately 3 mos. following the minigraft procedure	**Repigmentation:** All patients who underwent 1-mm minigrafting obtained >60% repigmentation. Mean repigmentation rate (range) [SD]: 81.6% (60%-95%) [11.0] In patients aged ≤ 12 years, mean repigmentation rate (range) [SD]: 87.9% (80%- 95%) [4.8]

Study details	Study population	Intervention	Notes
School of Medicine, university setting 6-32 mos. f/u			In patients aged ≥ 13 years, mean repigmentation rate (range) [SD]: 67.5% (60%-73%) [6.1] The differences between the results in those less than or older than 12 was statistically significant ($p<0.05$) **Side effects:** Darker pigmentations in the skin grafts than the surrounding skin were seen in 3 patients, and cobblestone appearance resulting from protrusion of the grafts were seen in 1 patient.
Kim, S. A. (2015). J Eur Acad Dermatol Venereol 29: 713-718.[151] Case series (retrospective) Korea Hospital setting ≥ 1 yr. f/u	N=111 Childhood facial vitiligo F: 50; M: 61 **Mean age (range), yrs:** 8.3 (1-15) **Duration of vitiligo range, yrs:** 1-10 yrs.	N + T N + S N + EL N + T + S N + T + EL N + S + EL N + T + S + EL N + EG N.B. Please see abbreviations below.	**Investigators global assessment:** 0(0% improvement); 1(<25% improvement); 2(25%-50% improvement); 3(50%-75%) improvement; 4(>75% improvement) **Mean Investigators Global Assessment:** N + T, 2.0 N + S, 3.0 N + E, 2.7 N + T + S, 2.2 N + T + E, 2.3 N + S + E, 2.5 N + T + S + E, 2.3 N + EG, 3.9 **Final visual outcome:** 1 (looking excellent); 2 (looking very good); 3 (looking good); 4 (looking fair); 5 (looking bad) **Mean Final Visual Outcome:** N + T, 2.0 N + S, 1.0 N + E, 1.5 N + T + S, 2.6 N + T + E, 1.9 N + S + E, 1.9 N + T + S + E, 2.1

Study details	Study population	Intervention	Notes
			N + EG, 1.5
Kim, S. R. (2018). JAMA Dermatology 154: 370-371.[167] USA Prospective case series University setting 3 mos.	Case 1: A female in her 30s with a 12-year history of vitiligo. Case 2: A male in his 50s with long-standing vitiligo.	Case 1: Tofacitinib 5mg twice daily + full-body NB-UVB twice weekly Case 2 – Tofacitinib 5mg twice daily + NB-UVB 2 to 3 times weekly Both patients were treated for 3 mos.	**Repigmentation:** Case 1: Nearly complete repigmentation on the face, ≥75% repigmentation of neck, chest, forearms, and shins. Case 2: 50% repigmentation of the face, and, after 6 mos., about 75% facial repigmentation.
Lee, J. (2016) Dermatology 232: 224-9.[152] Case series (retrospective) South Korea Hospital setting 6 mos. f/u	N=32 F: 14; M: 18 **Mean age (range), yrs:** 40.6 (20-75) **Mean (range) duration of vitiligo, yrs:** 12.6 (0.6-40)	Oral methylprednisolone (MPD) at a dose of 0.5 mg/kg administered on two consecutive days/week + NB-UVB thrice weekly Patients were treated for 3 mos.	**Attrition:** only two patients discontinued due to gastrointestinal side effects at 8 wks. **Repigmentation:** • Repigmentation ≥50% (>50%), 13 patients • Repigmentation ≥75% (>75%), 5 patients **Side effects, number of patients (%):** • Gastrointestinal, 4 (12.5) • Increased appetite, 2(6.3) • Flushing, 1(3.1)
Majid, I. (2009) Indian J Dermatol 54:124-7.[153] Case series (prospective) India Hospital setting 6 mos. f/u	N=400 Childhood vitiligo F: 266; M: 134 **Age range, yrs:** 18 mos. – 15 years **Mean (range) duration of vitiligo:** 4.3 mos. (1 week – 4.5 yrs)	MPD for 2 consecutive days every week, the dose used was 0.8mg/kg body weight with the maximum dose of 32mg each day. This was combined with once daily topical application of 0.01%	**Attrition:** 57 patients did not come to regular follow-up and were not assessed. **Repigmentation:** • Repigmentation ≥50%, 70 patients • Repigmentation >75% (> 90%), 41 patients **Side effects:** • Gastric irritation, 18 patients • Tinea capitis and/or corporis, 16 patients

Study details	Study population	Intervention	Notes
		fluticasone ointment at bedtime. Patients were treated for at least 6 mos.	• Precipitation of acne, 11 patients
Schallreuter, K. U. (2008). Int J Dermatol 47: 743-753.[161] Case series (retrospective) UK Hospital 8 – 12 mos. f/u	N=71 F: 45; M:26 **Mean age (range), yrs.:** 10.3 (2 – 14) **Vitiligo vulgaris on the face/neck,** 71/71 **Vitiligo vulgaris on the trunk,** 61/71 **Vitiligo vulgaris on the extremities,** 55/71	Pseudocatalase PC-KUS cream twice daily + NB-UVB 0.15 mJ/cm^2 once daily for 14 days, then twice daily for 4 wks. NB-UVB monotherapy daily was tested on 10 additional children over 6-months as a control.	**Repigmentation of face/neck:** • 100% repigmentation, 39.4% (28/71) • >75% repigemntation, 38 54% (38/71) **Repigmentation of trunk**: • >75% repigmentation, 78.8% (48/61) **Repigmentation of extremities:** • >75% repigmentation, 72.7% (40/55) Cessation of the disease was achieved in 99% (70/71) of patients receiving the combination therapy and 30% in the NB-UVB monotherapy control group. **Side effects:** No side effects were reported

Abbreviations: EL, excimer laser therapy; EG, epidermal graft; F, female; JEADV, Journal of the European Academy of Dermatology and Venereology; M, male; N, Nutritional therapy; S, systemic steroid pulse therapy or triamcinolone intralesional injection; MPD, Methylprednisolone; PC – KUS, pseudocatalase; SD, standard deviation; T, topical therapy; UVB, ultraviolet B; yrs, years; NB-UVB, narrow-band ultraviolet B.

Table 30: Summary of non-comparative studies investigating surgical therapies

Study details	Study population	Intervention	Notes
Altalhab, S., M. I. AlJasser, et al. (2019). J Eur Acad Dermatol Venereol 33(6): 1172-1176.[162] Retrospective case series Saudi Arabia Outpatient	N=602 (553 completed) F: 410; M: 192 **Mean (range) age, yrs.:** 24.25 (4.0 – 67.0) **Disease duration, yrs.:** > 8 yrs., 247; ≤ 8yrs., 306	Melanocyte-keratinocyte transplantation The area was anaesthetized with 2% lidocaine.	**Attrition:** 49/602 (553) **Repigmentation ≥ 75%** 84.3% **Relapse:** Body surface area < 1% (adjusted HR = 0.37; p = 0.04) and mechanical dermabrasion (adjusted HR = 0.26; p =0.03) were independently associated with lower rates of relapse. Non-segmental vitiligo (adjusted HR = 2.11; p =0.03) and fingertip involvement (adjusted

Study details	Study population	Intervention	Notes
6 yrs. f/u			HR = 3.75; p = 0.01) were independently associated with higher rates of relapse.
Bae, J. M. (2018). Journal of the American Academy of Dermatology 79: 720-727.e721.[163] Retrospective case series Korea Outpatient 6 mos. f/u	N=208 (230 lesions) F: 99; M: 109 **Median (range) age, yrs.:** 32.7 (5 – 68) **Median (range) duration of vitiligo, yrs.:** 9.5 (6 mos. – 47 yrs.)	Motorized 0.8-mm micro-punch grafting Treatment for a median of 6 mos.	**Complete repigmentation ≥ 90%** 67.4% **Repigmentation ≥ 75%** 78.7% **Adverse effects:** Colour mismatch (57/230 lesions) was prevalent on the hands and feet (OR 9.432 compared with the face and neck) and decreased gradually with time following surgery (p<0.001); cobblestone appearance (42/230 lesions), this was higher in; hyperpigmentation (26/230 lesions); perilesional halo (14/230 lesions)
Gan, E. Y. (2016). J AA D 75: 564-571.[154] Singapore Retrospective case series Hospital setting 12 mos. f/u	N=177 F: 97; M: 80 **Mean age (SD), yrs.:** 34.4 (15.3) **Mean duration of vitiligo:** 99 mos.	Non-cultured cellular grafting MultiClear targeted phototherapy set with UVB and UVA1 mode was initiated in patients who showed poor epidermal repigmentation by the 2nd follow-up visit, corresponding to < 25% of repigmentation over the grafted site.	Attrition: 21% of patients did not have data available; 140 patients had data available. **Repigmentation:** Good-excellent repigmentation (>50%) was present in 77% (n=108) of patients who had data available (n=140); repigmentation was maintained up to 60 mos. post-grafting, 83% (n= 19) of those remaining on active follow-up (n=23) sustaining good-excellent repigmentation. **Side effects:** Evaluation was limited due to the retrospective nature of the study and was reliant on the clinician's documentation. <10% of cases had post-inflammatory pigmentary changes at the donor site, and 5% developed hypertrophic scarring at the same area. None of the patients had postsurgical infection, and no scarring developed on the recipient sites.
Janowska, A. (2016). Int Wound J 13 Suppl 3: 47-51.[155]	N=5 F: 3; M: 2	Epidermal skin grafting	**Cosmetic outcome:** "Good" cosmetic outcome in four of five patients.

Study details	Study population	Intervention	Notes
Italy Prospective case series University 3 mos. f/u	**Mean (range) age, yrs.:** 40.2 (23 – 67)	NB-UVB was preformed twice per week for 2 mos. in four of five patients who showed minimal repigmentation in the after the first mo.	"Excellent" cosmetic outcome in one patient who achieved 100% repigmentation at 1-mo. follow-up. **Side effects:** Donor sites were fully healed without scarring within 14 days of harvesting and required no further treatment. Infection or Koebner phenomenon were not observed during the follow-up period.
Kachhawa, D. (2017). J Cutan Aesthet Surg 10: 81-85.[156] India Prospective case series Outpatient setting 6 mos. f/u	N=154 F: 85; M: 69 **Age range, yrs.:** 11 - 50 **Duration of vitiligo:** NR	Non-cultured non-trypsinised epidermal cell graft technique Dermabrasion was conducted using a micromotor dermabrader; in some cases, a manual dermabrader was used to obtain epidermal cells Oral antibiotics were given until complete healing of the recipient and donor site was achieved (14-18 days)	**Repigmentation:** Excellent improvement (≥75%) was achieved in 179 patches. Very good improvement (50-74%) was achieved in 114 patches Best improvement was seen on the thighs, face and trunk where 100%, 75% and 50% of the patches, respectively, showed excellent repigmentation. **Side effects:** Minor burning and pain at both the recipient and donor sites; secondary infection was observed in <5% of patients.
Kumar, P. (2018). Int J Dermatol 57: 245-249.[157] India Prospective case series Outpatient setting 6 mos. f/u	N=25 F: 15; M: 10 **Mean age (SD) [range], yrs.:** 24.5 (3.06) [18-36] **Mean (SD) [range] duration of vitiligo stability:** 60 (41.1) [18 – 120]	Extracted follicular outer root sheath cell suspension transplantation	**Repigmentation:** Good repigmentation (>75%) was achieved in eight patients; moderate repigmentation (50-75%) was achieved in six patients. The head and neck area showed better repigmentation compared with acral bony sites (p=0.61).

Study details	Study population	Intervention	Notes
Orouji, Z. (2018). J Dermatol Sci 89: 52-59.[158] Iran Prospective case series Clinic setting Up to 30 mos. f/u	N=300 F: 189; M: 111 **Mean age (SD) [range], yrs.:** 27.1 (9.7) [12-71] **Mean (SD) [range] duration of vitiligo, yrs.:** 12.0 (7.8) [1 – 41]	Epidermal cell transplantation Epidermal cell suspension prepared by processing a skin specimen from the patients' thigh-buttock junction.	**Repigmentation:** Nine months after transplantation, >50% repigmentation was achieved in 32.2% treated patches (p<0.001). Six months after cell transplantation, >50% repigmentation based on physician and patients' assessment was respectively achieved in 20.1% (213/1060) and 22.3% (149/667) of treated patches. Twelve months post-transplantation, >50% repigmentation based on physician and patients' assessment was respectively achieved in 34.90% (199/571) and 43.1% (134/311) of treated patches. Pigmentation loss was observed in 20.7% (n = 219) of treated patches. This occurred at a mean of 9.20 (6.11) months post transplantation; this occurred mostly during the first year (68.5%). **Side effects:** At the recipient site, mild erythema was observed which often resolved spontaneously within 2hrs; mild swelling and mild ecchymosis was observed in all patients, particularly on sites with looser skin. At the donor site, patients experienced pain for 24hrs after the procedure; post-inflammatory hyper-pigmentation was observed in 32 patients; Koebner phenomenon was observed in 6 patients.
Ramos, M. G. (2017). An Bras Dermatol 92: 312-318.[159] Brazil Prospective case series Setting, NR 3 – 12 mos. f/u	N=20 F: 14; M: 6 **Mean age (SD) [range], yrs.:** 30.75 (12.2) [10-50] **Duration of vitiligo:** NR	Transplantation of non-cultured melanocyte/keratinocyte cell suspension This was performed in one or two sessions.	**Repigmentation:** Excellent repigmentation (≥ 90%) was experienced in 25% of patients Good repigmentation (50 – 89%) was experienced in 50% of patients The best responses were observed in the face and neck regions, excellent repigmentation in 37.5% and good repigmentation in 50% of patients. **Side effects:** ○ Koebner phenomenon experienced in one patient; another patient presented hyperpigmentation.

Study details	Study population	Intervention	Notes
Shashikiran, A. R. (2018). Indian Journal of Dermatology, Venereology and Leprology 84: 203-205.[144] Prospective case series India Hospital 6 mos. f/u	N=39 (100 patches) F: 25; M: 14 **Age range, yrs.:** 13 – 44 **Mean (range) duration, yrs.:** 4.9 (1.2 – 11.5)	Topical fluorouracil 5% cream was applied on the patch with a 26-G needle.	**Repigmentation > 75%** 49% of patches **Repigmentation 50 – 75%** 26% of patches **Adverse effects** Pain (100%); erythema and itching (52%); ulceration (6%); koebnerization (1%) Repigmentation was stable throughout the follow-up period of 6 mos. Except in patient who had recurrence of depigmentation and development of new lesions.
Silpa-Archa, N. (2017). J Am Acad Dermatol 77: 318-327.[160] USA Retrospective case series Hospital setting 12 - 72 mos.; median, 24 mos. f/u	N=83 F: 32; M: 51 **Mean age (range), yrs.**: 9 – 60 **Duration of vitiligo:** NR	Melanocyte-keratinocyte transplantation (MKT) Recipient sites were denuded with 1 pass of CO_2 laser.	**Repigmentation** **Excellent (91 – 100%)** Segmental/focal vitiligo, 58%; Non-segmental vitiligo, 36% **Very good (76-90%)** Segmental/focal vitiligo, 13%; Non-segmental vitiligo, 18% **Good (51-75%)** Segmental/focal vitiligo, 18%; Non-segmental vitiligo, 10% *N.B. this study also included patients with physical leukoderma, piebaldism, and Halo nevi – only results for patients with vitiligo are reported here.*

Abbreviations: F, female; M, male; SD, standard deviation; MKT, melanocyte-keratinocyte transplantation; NB-UVB; narrow band ultraviolet B; NR, not reported; standard deviation; USA, united states of America; UVA, ultraviolet A; yrs., years.

Table 31: Summary of non-comparative studies investigating psychological therapies

Study details	Study population	Intervention	Notes
Jha, A. (2016). Indian J Dermatol, Venereol Leprol 82: 308-310.[146] Prospective case series India Community setting 12 wks. f/u	N=13 F: 4; M: 9 **Mean (SD), yrs.:** 25.8 (6.3) **Duration of vitiligo, yrs.:** NR	Session 1: Psycho-education – given once (on the first day of therapy), lasting 20-25 minutes. Session 2: Breathing, relaxation, and imagery – given 3 times/day Session 3: Self-statements – given 6-10 times a day Session 4 & 5: Exposure and desensitization – given 1-3 times/day Five weekly sessions given by a dermatology trainee who had been trained by a clinical psychologist.	Attrition: five patients were lost to follow-up; authors attributed a significant dropout rate to the use of a non-pharmacological intervention. The authors observed that women who completed the treatment were self-motivated and had a better understanding of their disease. After 5 sessions, all eight patients showed an improvement in DLQI; four of these patients had a reduction that was meaningfully different at 12-week follow-up. After 5 sessions, five of eight patients had a significant/meaningful reduction in their Skindex-16 scores. After 5 sessions, seven of eight patients showed an improvement in the mood charts; one patient showed a worsening of mood scores, this was attributed to the increase number of skin lesions at the time. Only one patient had repigmentation, but this did not reach 50%.

Abbreviations: DLQI, dermatology life quality index; F, female; M, male; NR, not reported; SD, standard deviation; wk., week; yrs., years

Table 32: Summary of non-comparative studies investigating skin camouflage therapies

Study details	Study population	Intervention	Notes
Chen, D. (2019). PloS one 14: e0210581.[166] Prospective case series China Hospital	N=854 F: 471; M: 413 **Mean (SD) age, yrs.:** 38.88 (13.10) **Mean (SD) DLQI score:** 5.83 (5.75)	An online survey in vitiligo patients who had been using camouflage for > 1 mo. Median duration of camouflage therapy, 50 mos. (1 – 216)	**DLQI** DLQI score 0-1 signifying no effect, 228/854 (25.8%); 2 -5 signifying small effect, 294/854 (33.3%); 6 – 10 signifying a moderate effect, 198/854 (22.4%); 11 – 21 signifying a large-to-extremely large effect, 164/854 (18.5%) Overall mean (SD) [range] DLQI, 5.83 (5.75) signifying it has a small to moderate effect on the patients' QoL. Mean (SD) DLQI scores for the six domains: daily activities, 1.47 (1.52); leisure, 1.47 (1.53); symptoms and feelings, 1.25 (1.14); personal relationships, 0.63 (1.22); work and school, 0.51 (0.88); treatment, 0.49 (0.79) The highest DLQI was found in "daily activities" followed by "leisure" and "symptoms and feelings" Significant impairment of QoL, 40.9% **Patient satisfaction:** 82/854 (9.3)
Ongenae, K. (2005). Dermatology 210: 279-285.[199] Case series (prospective) Belgium Vitiligo association, community setting On average the camouflage was used for 3.8 mos. and the DLQI was assessed after at least 1 month's use	N=78 **Mean age (SD) [range], yrs:** 40.9 (13) [16-68] **Mean vitiligo duration (SD) [range], yrs:** 18.8 (13.3) [1-57]	Patients were given a stigmatisation questionnaire and the DLQI to complete. The patients consequently received a second questionnaire together with a camouflage sample matching their skin complexion and were asked to return the second	**DLQI, the higher the score the more QoL is impaired** Involvement of (1-6) localizations (N=37; DLQI mean 3.5; SD, 3.0) resulted in a significantly ($p<0.0001$) lower DLQI score compared with involvement of all 7 localizations (N= 41; DLQI mean 10; SD, 5.7). The DLQI score was found to be significantly correlated with the total severity score (Pearson $r = 0.52$, $p<0.0001$) and with self-assessed disease severity in different localizations ($p=0.0007$ to $p = 0.02$), indicating that visibility is not a major determinant of the DLQI score (note the negative correlation). But this is not observed for face/head/neck localizations. A significant ($p=0.006$) improvement was observed of the DLQI score after use of camouflage: mean (SD) DLQI before, 7.3 (5.6); after, 5.9 (5.2).

Study details	Study population	Intervention	Notes
		questionnaire after at least 1 mo. use of the sample. Out of the 78 patients, 62 patients (response rate of 82%) duly applied the camouflage sample and returned the second questionnaire.	When comparing DLQI before (mean, 4.3; SD, 3.1) and after camouflage (mean, 3.9; SD, 3.4) in patients with an initial score <10 (N=42) versus DLQI before (mean, 14.8; SD, 2.8) and after camouflage (mean, 10.9; SD, 5.6) in those with a DLQI score >10 (N=18) there is a significant improvement (p= 0.0005).
Padilla-España, L. (2014) Actas Dermosifiliogr 105: 510-4.[137] Case series (prospective) Spanish Hospital 2 wks. f/u	N=6 F: 5; M: 1 **Age range, yrs:** 10-15	Camouflage therapy workshop. A family member was present so that both the child and the family member could learn the basics and be able to apply the cosmetic at home.	Only three of the six patients had vitiligo (segmental). **QoL:** **Female age 10 yrs.** cDLQI before session, 13; cDLQI after session, 4 **Female age 13 yrs**. cDLQI before session, 19; cDLQI after session, 7 **Female age 15 yrs.** cDLQI before session, 4; cDLQI after session, 1 All three patients were independently using cosmetic camouflage 6 months after the camouflage therapy workshop.
Rajatanavin, N. (2008). Int J Dermatol 47: 402-406.[138] Part 1: prospective case series Part 2: retrospective case series Thailand	N=20 F: 14; M: 6 **Mean age (range), yrs:** 44.25 (7-67)	Part 1: each subject was recommended to apply three different DHA creams that contain 3.5%, 4.2%, and 5% DHA on both inner arms, which are less	**Part 1:** Part 1 was conducted on healthy volunteers, so the results have not been reported in this table. **Part 2:** Eight of the 20 patients observed that the skin took 8 hours to develop pigment darkening. Three of the 20 patients did not use DHA because of dissatisfaction with the product, and two of the three patients refused to score the efficacy. Sixteen of the 20 patients reported moderate to marked satisfaction.

Study details	Study population	Intervention	Notes
Hospital Treatment duration/follow-up: NR		pigmented than other skin areas. Part 2: each patient was instructed to apply 6% DHA cream (pharmacy preparation) as self-tanners on vitiliginous area.	The reasons for not using DHA were irregular brownish staining and no staining at all. None of the patients experienced undesirable side effects.

Abbreviations: DHA, dihydroxyacetone; cDLQI, children's dermatology quality of life index; DLQI, dermatology quality of life index; F, female; M, male; NR, not reported; QoL, Quality of Life; SD, standard deviation; yr, year.

Table 33: Summary of non-comparative studies investigating complementary therapies

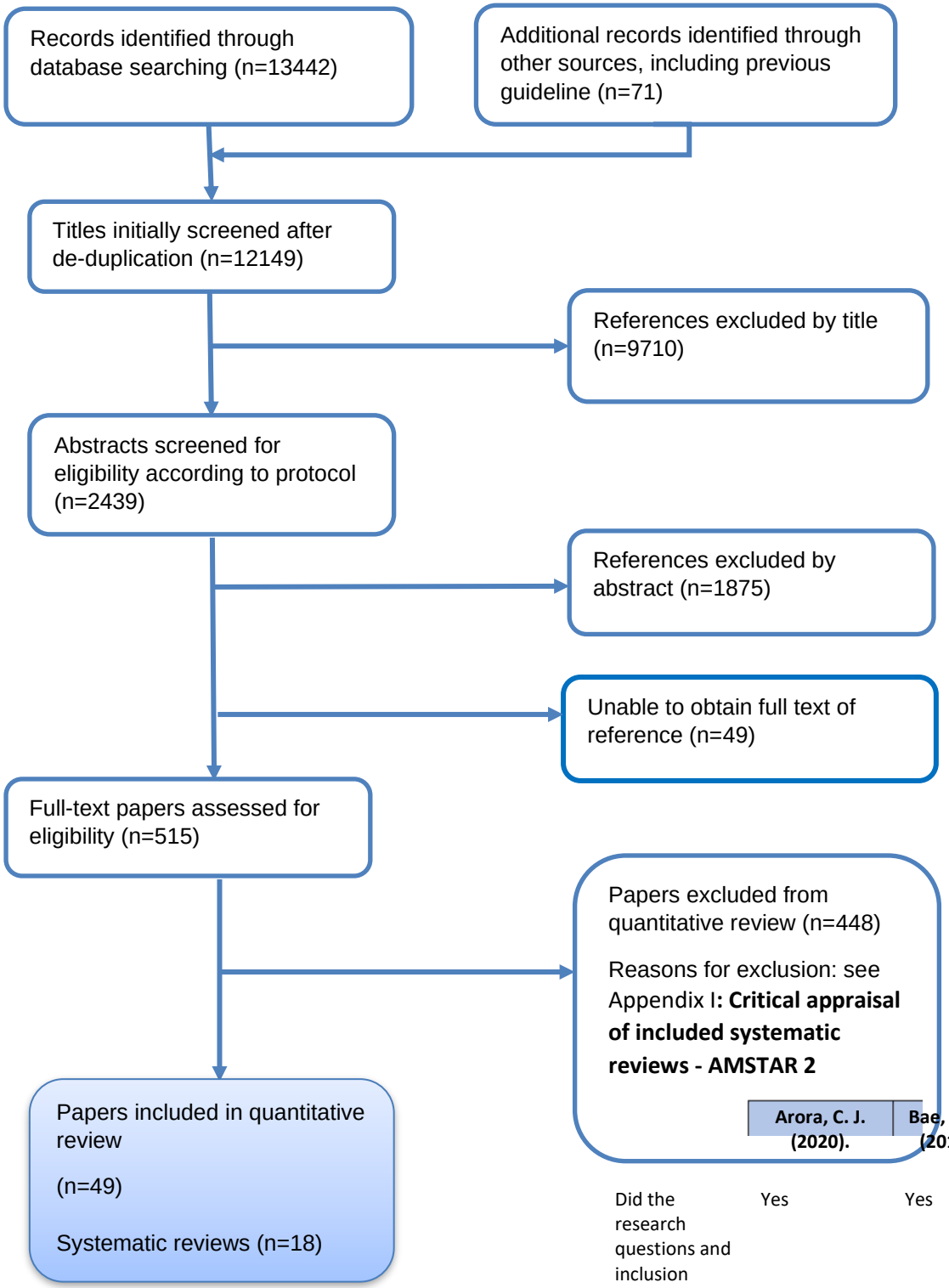
Study details	Study population	Intervention	Notes
Czarnowicki, T. (2011). J Eur Acad Dermatol Venereol 25: 959-63.[139] Case series (retrospective) Germany Medical centre 4-7 wks. f/u	N=436 F: 306; M: 130 **Mean age (SD) [range]:** 36.2 (16.4) [3.5-81.4] **Duration of vitiligo, n (%):** <10 yrs, 180 (41.3) 10-19 yrs, 127 (29.1) 20-49 yrs, 116 (26.6) ≥ 50 yrs, 13 (3.0)	Dead sea climatotherapy Treatment time, n (%): <4 wks., 123(28.2%) 4 wks., 171(39.2%) 5-7 wks., 142(32.6%) The treatment protocol included 28 days of bathing at the Dead Sea for a 4-wk stay.	**Repigmentation:** • Repigmentation ≥50% (>50%), 17 patients Patients with skin phototype II were shown to have the greatest improvement compared with other skin types (p = 0.002) Those arriving in April-June had the highest chances of improvement (p=0.002) Longer duration of treatment was found to increase the probability of improvement (p<0.001) Patients were contacted 1-2 years following treatment, 30 patients were successfully reached and asked whether the repigmentation process had continued. The following was reported: • Overall, 83% of these patients responded positively • Repigmentation was maintained in 63.3% of patients who responded positively, of which 23.3% reported partial maintenance • In 13.3% the repigmentation was lost

Study details	Study population	Intervention	Notes
Hemanta Kumar, P. (2012) Int J Res Ayurveda Pharm 3: 868-71.[140] Case series (prospective) India Research institute 6 mos. f/u	N=20 F: 8; M: 12 **Age, yrs:** >15 **Duration of vitiligo, yrs:** 1-7	A small needle prick was given to the affected part prior to the application of the leeches, the leeches sucked blood till they left spontaneously. Leeches were applied weekly to the vitiligo patch for 6 mos.	**Repigmentation:** • Repigmentation ≥50%, 17 patients • Repigmentation ≥75%,10 patients
Lopes, C. A. C. (2011) J Plast Dermatol 7: 5-10[141] Case series (prospective) Brazil Hospital 18 mos. f/u	N=42 F: 31; M: 11 **Age, yrs**: >18 **Duration of vitiligo:** NR	Vitalog (containing 80 mg of *Stachytarpheta cayensensis Vahl* aqueous dried extract) three times daily for 18 mos.	**Attrition:** four patients dropped out **Repigmentation ≥75% (>75%)** • Arms (15 lesions) • Legs (13 lesions) • Knee (9 lesions) • Face (5 lesions) • Front (3 lesions) • Neck (8 lesions) • Chest/breast (10 lesions) • Back (6 lesions) • Total, 69/99 lesions achieved ≥75% repigmentation
Sarac, G. (2019). Dermatologic therapy: e12949.[164] Prospective case series Turkey Outpatient clinic 6 mos. f/u	N=33 (47 patches) F: 18; M: 15 **Mean (SD) [range], yrs.:** 31.94 (9.88) [20 – 58] **Mean (SD) [range] disease duration, mos.:** 17.6 (12.86) [2-36]	Nigella satvia seed oil applied topically to the hands, face, and genital region twice daily Treatment for 6 mos.	**Repigmentation ≥ 50%** 10/23 (43.5%)

Study details	Study population	Intervention	Notes
Shraddhamayananda, S. (2012); Asian J Pharm Clin Res 5: 33-5[142] Case series (prospective) India Outpatient 24 mos. f/u	N=200 F: 129; M: 71 **Age group, n (%):** <10 yrs, 11(5.5) 10-20 yrs, 127(63.5) 20-50 yrs, 58(29.0) >50 yrs, 4(2.0) **Duration of vitiligo:** NR	All patients were administered one of the following homeopathic medicines with dilutions 200/1000: calc. carb., lycopodium, lachesis, mezerium, nat. mur., sepia, ars.s.fl., ars. alb. Follow-up was weekly/monthly or as per decision of the consultant.	**Repigmentation:** • Repigmentation ≥50%, 190 patients • Repigmentation 100%, 140 patients At 10-12 months the largest proportion of patients achieved ≥50% repigmentation (58/200) and 100% repigmentation (54/190).
Widhiati, S., I. Julianto, et al. (2019). Dermatology Reports 11(S1): 11-13. [165] Prospective case series Indonesia Hospital 24 wks. f/u	N=7 F: 5; M: 2 **Mean (range) age, yrs.:** 33.4 (18 – 78) **Range duration of vitiligo stability, mos.:** 13 – 180	Autologous NCES combined with PRF	**Repigmentation > 90%** 66.67% **Repigmentation 75 – 90%** 16.67% **Repigmentation 50% - 75%** 13.3%

Abbreviations: M, male; F, female; f/u, follow-up; mos., months; NCES, non-cultured epidermal cell suspension; NR, not reported; PRF, platelet rich fibrin; QoL, quality of life; SD, standard deviation; yr., year

Appendix H: PRISMA diagram - study selection



	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Char (2
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to	Yes	Yes	Partially Yes	No

Appendix I: Critical appraisal of included systematic reviews - AMSTAR 2

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Partially Yes	No	Partially Yes	Partially Yes	No	No	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No	Yes	No	No	No	No – a mixture of study designs included.	Yes	No – a mixture of study designs included.	No
Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes – MEDLINE, EMBASE, Cochrane, and reference lists were scanned.	Partially Yes	Yes – Cochrane, EBM reviews, MEDLINE, CNKI, CEPS, Chinese Biomedical Literature database, WANGFAN.	Yes – PubMed, EMBASE, and the Cochrane library databases. All identified articles were screened for cross references.	Partially Yes– PubMed, Embase, EBSCO, ISI web of knowledge and reference lists were scanned.	Yes –EMBASE, MEDLINE, Scopus, Cochrane, and clinical trials.	Partially Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
					All reference lists were also scanned.				
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Unclear – two authors independently extracted the data, but not mentioned if two independent authors performed study selection.	Yes	Yes	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Partially Yes – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of studies excluded	Yes	No	Partially Yes – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of studies excluded	No	Partially Y – the authors gave reasons for exclusion of studies after full-text review, but they did not provide references for these studies.	No	No	Partially Yes – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of studies excluded
Did the review authors describe the included	Yes	Yes	Yes	Partially Yes	Yes	Yes	No	Yes	Partially Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
studies in adequate detail?									
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes – the authors provided a RoB summary.	No	Yes	Yes – the authors provided a RoB summary.	Yes – the authors provided a RoB summary.	No	Yes – the authors provided a RoB summary.	Yes
Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	Yes – the included studies did not report source of funding.	No	No	No	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes – the meta-analysis was performed using the generic inverse variance method.	Yes – authors conducted a single-arm proportional meta-analysis.	Yes	N – the authors combined studies which used five different oral CHM formulas with great variation in terms of ingredients.	Yes	Partially Yes – the authors compared various combinations.	Yes – the review authors review authors used the Mantel-Haenszel method with random-effects weighting.	Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
For non-randomized studies of intervention, did the authors do the following: (1) Justify combining data in a meta-analysis (2) Use an appropriate weighted technique to combine study results, adjusting for heterogeneity if present (3) Statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available (4) Report separate summary estimates for RCTs and NRSI separately when both were included in the review	NA – no meta-analysis conducted of NRSI	NA – only RCTs.	No	No	NA – Only RCTs.	No – no explanation given for combining study designs.	NA – only RCTs.	NA – only RCTs.	No

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	No	No	No	Yes	No	Yes	No
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Partially Yes – the authors do report on the RoB, but the impact on the results are not discussed in detail.	No	Yes	Yes	Yes	No	Partially Yes- the authors do report on the RoB, but the results are not discussed in detail.	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias)	No	Yes	No	Yes	Yes	Yes	Yes	NA – publication bias was not assessed due to the small number of studies.	Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
and discuss its likely impact on the results of the review?									
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes - no conflicts of interest to declare	Yes – none declared.	Yes – grant from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science.	Yes – the authors received no financial support	Yes – no conflict of interest declared.	Yes – none declared; the authors had no funding source providing the financial support for the conduct of the research.	Yes – none declared	Yes – none declared	Yes – no conflicts of interest to declare

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?	Partially Yes – protocol not registered	No	No	Partially Yes	No	No	Partially Yes	Yes	Partially Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	No	No	No – a mixture of study designs included.	No	Yes – inferred	Yes	Yes	Yes	No
Did the review authors use a comprehensive literature search strategy?	Yes	Partially Yes – PubMed, EMBASE, Cochrane, Web of Science, and reference lists were scanned.	Yes – MEDLINE, EMBASE, Cochrane, clinical trials and reference lists were scanned.	Partially Y – the authors searched MEDLINE, EMBASE, Cochrane, DARE, and HTAs. The authors also searched for	Yes	Partially Yes – PubMed, Embase, CBMdisc, CNKI, WANFANG and CQVIP. The authors	Yes –EBM reviews, allied and complementary medicine, CINAHL, EMBASE, MEDLINE, Ovid HealthStar.	Yes	Partially Yes – the PubMed and Cochrane library were independently searched. Reference lists of prior reviews, systematic reviews

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
				retractions of studies included in the review. The authors did not provide search terms used.		also performed a manual search of reference lists.			and trials were also checked.
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	No	Yes	Yes	Partially Y– the assessment process was completed by one author, in consultation with another author.	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Partially Y – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of studies excluded	No	No	No	Yes	No – the authors state the number of excluded studies, but they do not provide a list.	No	Yes	No
Did the review authors describe the included studies in adequate detail?	Yes	Partially Yes	Partially Yes	Partially Yes	Partially Yes	Partially Yes	Yes	Yes	Partially Yes

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Yes - the authors provided a RoB summary	Yes – the authors provided a RoB summary	Yes – the authors performed GRADE	Yes	Yes – the authors provided a RoB summary.	Yes – the Jadad scale was used, the authors provided a summary of the results.	Yes	Yes – the authors assessed the RoB.
Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No	No	No	No	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes – fixed effects model used due to no significant heterogeneity.	NA – no meta-analysis	No	Yes	Yes	NA – the authors stated that it was not possible to pool the data from the studies due to the wide differences in outcome measures.	Yes	No – the review authors used random-effects model, but it may have been more appropriate to use fixed-effect due to the small number of studies.
For non-randomized studies of intervention, did the authors do the following: (1) Justify combining data in a meta-analysis	No	NA – only RCTs.	NA – no meta-analysis.	NA – no meta-analysis.	No	NA – only RCTs.	NA – no meta-analysis.	NA – Only RCTs.	NA – only RCTs.

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
(2) Use an appropriate weighted technique to combine study results, adjusting for heterogeneity if present (3) Statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available (4) Report separate summary estimates for RCTs and NRSI separately when both were included in the review									
If meta-analysis was performed, did the review authors assess the potential impact of RoB in	No	Yes	NA- no meta-analysis.	NA – no meta-analysis.	No	Partially Yes	NA – no meta-analysis.	Yes	No

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
individual studies on the results of the meta-analysis or other evidence synthesis?									
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	Partially Y- the authors do report on the RoB, but the results are not discussed in detail.	Partially Y- the authors do report on the RoB, but the results are not discussed in detail.	No	Yes	Yes	Yes	Yes	No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	NA – publication bias was not assessed due to the small number of studies.	NA – no quantitative synthesis was conducted.	NA – no quantitative synthesis was conducted.	Yes	Yes	No	Yes	Yes

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes – no conflicts of interest to declare	Yes – the project was funded by the National Natural Science Foundation of China.	Yes – none declared	Yes – none declared.	No	Yes – none declared.	Yes – none declared; during the duration of this project Szczurko received a Complementary and Alternative Medicine in Paediatrics Masters Scholarship from the Sick Kids Foundation; Boon was funded as a Canadian Institutes of Health Research New Investigator.	Yes	Yes – none declared. The work was supported (not stated how) by the Vitiligo Research foundation; public welfare programme, ministry of health, China.

Abbreviations: CHM, Chinese herbal medicine; NA, not applicable; N, no; RCT, randomized controlled trial; RoB, risk of bias; Y, yes

Appendix J: Papers excluded from quantitative analysis

Topical treatments

Reference	Reason for exclusion
Abdou, A. G. (2017). J Immunoass Immunoch38: 523-537.	Outcomes – not relevant
Abd-Elazim, N.E. (2019) J Cosmet Dermatol 19: 1447-1455	Within-patient study (See Appendix G)
Abdelwahab, M., M. Salah, et al. (2020). Clin Cosmet Investig Dermatol 13: 77-85.	Outcomes (repigmentation not reported in way that meets the protocol criteria)
Akdeniz, N. (2014). J Dermatolog Treat 25: 196-199.	Included in Whitton, Cochrane Database Syst 2015
Ameen, M. (2001). Br J Dermatol 145: 476-479.	Comparative study; no extractable data (See Appendix F)
Anbar, T. S. (2015). Int J Dermatol 54: 587-593.	Within-patient study (See Appendix G)
Asilian, A. (2009). JPAD 19: 151-157.	Within-patient study (See Appendix G)
Bagherani, N. (2016). Dermatol Ther 29: 137-138.	Summary of Nistico, S. (2015)
Bagherani, N. (2016). Dermatol Ther 29: 288.	Summary of Sharquie, K. E. (2015)
Bayoumi, W. (2012). Br J Dermatol 166: 208-211.	Included in Whitton, Cochrane Database Syst 2015
Bilaç, D. B. (2009). J Eur Acad Dermatol Venereol 23: 72-73.	Case report
BinSaif, G. A. (2010). J Drugs Dermatol 9: 1092-1094.	Unable to obtain full text
Chang, H. C., Y. P. Hsu, et al. (2020). J Am Acad Dermatol 82(1): 243-245.	Systematic review - published as a letter, lack of information reported.
Chiaverini, C. (2002). J Eur Acad Dermatol Venereol 16: 137-138.	Outcomes – percentage repigmentation is below the threshold
Choi, C. W. (2008). J Dermatol 35: 503-507.	Outcomes
Clayton, R. (1977). Br J Dermatol 96: 71-73.	Outcomes – not reporting repigmentation at the threshold
Cosekun, B. (2005). Eur J Dermatol 15: 88-91.	Unable to obtain full text
Dang, Y. P. (2016). Dermatol Ther 29: 126-133.	Exclude as indirect comparisons were made and there were problems with the methods of analysis.
de la Fuente-Garcia, A. (2014). Indian Dermatol Online J 5: 117-121.	Outcomes – the study defines the efficacy outcome as a lower threshold (>25% repigmentaton)
de Menezes, A. F. (2017). Pediatr Dermatol 34: 13-24.	Outcomes – not relevant
Ermis, O. (2001). Br J Dermatol 145: 472-475.	Included in Whitton, Cochrane Database Syst 2015
Eryilmaz, A. (2009). J Eur Acad Dermatol Venereol 23: 1347-1348.	Within-patient (See Appendix G)

Reference	Reason for exclusion
Farajzadeh, S. (2009). Pediatr Dermatol 26: 286-291.	Included in Whitton, Cochrane Database Syst 2015
Farajzadeh, S. (2013). J Mazandaran Univ Med Sci 23: 238-248.	Foreign language
Fatemi-Naeini, F. (2014). J Isfahan Med Sch, 31 (Suppl 269) 2309-14	Unable to obtain full text
Grimes, P. E. (2016). J Drugs Dermatol 15: 703-710.	Unable to obtain full text
Halder, R. M. (2012). Arch Dermatol 148: 1432.	Outcomes – not quantified
Handjani, F. (2017). Dermatol Pract Concept 7: 31-33.	Outcomes – repigmentation defined as a lower threshold (25% repigmentaiton)
Hartmann, A. (2005). Int J Dermatol 44: 736-742.	Within-patient study (See Appendix G)
Hartmann, A. (2008). Acta Derm Venereol 88: 474-479.	Within-patient study (See Appendix G)
Hartmann, A. (2014). Acta Derm Venereol 94: 585-587.	Outcomes - not reporting repigmentation at the threshold
Ho, N. (2011). Br J Dermatol 165: 626-632.	Included in Whitton, Cochrane Database Syst 2015
Jha, A. K. (2016). Clin Exp Dermatol 41: 821-822.	Outcomes – not relevant
Jha, A. K. (2016). J Eur Acad Dermatol Venereol 30: 1247-1248.	Study design - case report
Jha, A. K. (2018). J Cosmet Dermatol 17: 437-440.	Population <10 patients
Joshipura, D. (2018). JAmAcad Dermatol78: 1205-1207.e1201.	Population <10 patients
Jprn, U. (2018). Http://www.who.int/trialsearch/trial2.aspx?Trialid=jprn-umin000031358.	Clinical trial; unpublished data
Juan, D. (2011). J Dermatol 38: 1092-1094.	Within-patient study (See Appendix G)
Kandil, E. (1974). Br J Dermatol 91: 457-460.	Included in Whitton, Cochrane Database Syst 2015
Kathuria, S. (2012). Indian J Dermatol Venereol Leprol 78: 68-73.	Included in Whitton, Cochrane Database Syst 2015
Kawalek, A. Z. (2004). Dermatol Surg 30: 130-135.	Included in Whitton, Cochrane Database Syst 2015
Khalid, M. (1995). Int J Dermatol 34: 203-205.	Included in Whitton, Cochrane Database Syst 2015
Köse, O. (2010). J Dermatolog Treat 21: 133-139.	Included in Whitton, Cochrane Database Syst 2015
Kumaran, M. S. (2006). J Eur Acad Dermatol Venereol 20: 269-273.	Included in Whitton, Cochrane Database Syst 2015
Kwon, H. B. (2013) J Drugs Dermatol, 12; e63-7.	Unable to obtain full text
Lepe, V. (2003). Arch Dermatol 139: 581-585.	Included in Whitton, Cochrane Database Syst 2015

Reference	Reason for exclusion
Li, J. C. (2009). Clin Exp Dermatol 34: e489-490	Case report
Lubaki, L. J. (2010). Arch Dermatol Res 302: 131-137.	Non-comparative
Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Naini, F. F. (2012). J Res Pharm Pract 1: 77-80.	Outcomes – not relevant
Nisticò, S. (2012). Photomed Laser Surg 30: 26-30.	Included in Whitton, Cochrane Database Syst 2015
Nowroozpoor Dailami, K., A. Hosseini, et al. (2020). Dermatol Ther 33(1): e13175.	Outcomes
Oh, S. H. (2011). J Am Acad Dermatol 65: 428-430.	Included in Whitton, Cochrane Database Syst 2015
Paracha, M. M. (2010), J Postgrad Med Inst 24: 115-121.	Included in Whitton, Cochrane Database Syst 2015
Park, O. J. (2016). Clin Exp Dermatol 41: 236-241.	Outcomes – not relevant
Parsad, D. (2009) Pigment Cell Melanoma Res	Editorial
Radakovic, S. (2009). J Eur Acad Dermatol Venereol 23: 951-953.	Included in Whitton, Cochrane Database Syst 2015
Rojas-Urdaneta, J. E. (2007), Invest Clin: 21-31.	Foreign languageIncluded in Whitton, Cochrane Database Syst 2015
Rokni, G. R. (2017). J Adv Pharm Technol Res 8: 29-33.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Rothstein, B. (2017). J Am Acad Dermatol 76: 1054-1060 e1051.	Outcomes – not relevant
Roy, P. (2016). Mymensingh medical journal: MMJ 25: 620-627.	Study design: follow-up not reported
Sahni, K. (2014). Indian Dermatol Online J 5: 164-166.	Included in Whitton, Cochrane Database Syst 2015
Sanclemente, G. (2008). J Eur Acad Dermatol Venereol 22: 1359-1364.	Included in Whitton, Cochrane Database Syst 2015
Sendrasoa, F. A., I. M. Ranaivo, et al. (2019). Int J Dermatol 58(8): 908-911.	Sufficient higher-quality evidence available
Shahmoradi, Z. (2012). J Res Med Sci 17: S17-S23.	Outcomes; no extractable data
Shashikiran, A. R. (2018). Indian J Dermatol Venereol Leprol 84: 203-205.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Silpa-Archa, N. (2016). Dermatologica Sinica 34: 177-179.	Within-patient study (See Appendix G)
Silverberg, J. I. (2011) J Drugs Dermatol, 10:507-10	Unable to obtain full text
Stinco, G. (2009). Eur J Dermatol 19: 588-593.	Included in Whitton, Cochrane Database Syst 2015

Reference	Reason for exclusion
Stinco, G. (2013). Dermatol Ther (Heidelb) 3: 95-105.	Outcomes – not in a format that matches the protocol
Wang, E. (2014). J Am Acad Dermatol 71: 391-393.	Case reports
Wazir, S. M. (2010). JPAD 20: 89-92.	Included in Whitton, Cochrane Database Syst 2015
Westerhof, W. (1999). Arch Dermatol 135: 1061-1066.	Included in Whitton, Cochrane Database Syst 2015
Xing, C. (2012) J Drugs Dermatol, 11: e52-4	Unable to obtain full text
Yaghoobi, R. (2011). BMC Dermatol 11: 7.	Included in Whitton, Cochrane Database Syst 2015
Zahoor, M. (2017). Journal of Pakistan Association of Dermatologists 27: 30-36.	Outcomes – not relevant

Depigmentation therapies

Reference	Reason for exclusion
Akakpo, A. S. (2016). Ann Dermatol Venereol 143: 197-201.	Population - patient population is not specific to vitiligo
AlGhamdi, K. M. (2011). J Eur Acad Dermatol Venereol 25: 749-757.	Study design – review; not systematic
Boukari, F. (2014) J Eur Acad Dermatol Venereol 28: 374-7	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Di Nuzzo, S. (2010). Clin Exp Dermatol 35: 215-216.	Case report
Durham, A. B. (2012). Dermatol Surg 38: 1563-1565.	Case report
Grimes, P. E. (2017). Dermatologic clinics 35: 219-227.	Study design – review; not systematic
Gupta, D. (2012). Indian J Dermatol Venereol Leprol 78: 49-58.	Study design – review; not systematic
Kim, S. (2016), J Cosmet dermatol 15: 16-23.	Outcomes – not relevant
Komen, L. (2013) Br J Dermatol 169: 1246-51	Retrospective case series (See **Error! Reference source not found.**)
Majid, I. (2013) J Cutan Aesthet Surg 6: 93-6	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Majid, I. (2017). Lasers Med Sci 32: 851-855.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Malathi, M. (2013). Indian J Dermatol Venereol Leprol 79: 842-846.	Study design – review; not systematic
Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Rordam, O. M. (2012). J Clin Aesthet Dermatol 5: 36-39.	Case report

Seneschal, J. (2014). Exp Dermatol 23: 879-880.	Editorial
Tan, E. S. (2015) Br J Dermatol 172: 1662-4	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
van Geel, N. (2015) J Eur Acad Dermatol Venereol 29: 121-7	Within-patient study (See Appendix G)

Systemic therapies

Reference	Reason for exclusion
Abdelmaksoud, A. (2019). DermatolTher: e12870.	Study design; letter
Abu-Raghif, A. R. (2013). Asian J Pharm Clin Res 6: 127-130.	Outcomes- re-pigmentation reported as VASI score; no extractable data.
Agarwal, S. (2005). Br J Dermatol 153: 163-166.	Included in Whitton, Cochrane Database Syst 2015
Alghamdi, K. M. (2012) J Drugs Dermatol, 11: 534-9	Unable to obtain full text
Bagherani, N. (2015). Dermatol Ther 28: 104.	Outcomes; no extractable data.
Bunker, C. B. (2019). J Eur Acad Dermatol Venereol 33: e20.	Case report
Dell'Anna, M. L. (2007). Clin Exp Dermatol 32: 631-636.	Included in Whitton, Cochrane Database Syst 2015
Elkady, A. (2017). JAAD Case Reports 3: 477-479.	Study design (case report); outcomes
Garza-Mayers, A. C. (2017). J Drugs Dermatol 16: 705-706.	Not available; case series, n=3
Karagüzel, G. (2016). Clinical nutrition ESPEN 15: 28-31.	Unable to obtain full text
Khondker, L. (2013). Mymensingh Med J 22: 761-766.	Unable to obtain full text
Konstantinova, V. A., O. Y. Olisova, et al. (2019). Clin Cosmet Investig Dermatol 12: 911-917.	Study design; n < 10 (n = 7)
Lee, D. Y. (2010) J Dermatol, 37: 1057-9	Outcomes – not relevant
Lee, Y. (2007) Clin Exp Dermatol, 32:499-501	Outcomes – not relevant
Li, L. (2016). J Cosmet Laser Ther 18: 182-185.	NA
Liu, L. Y. (2017). J Am Acad Dermatol 77: 675-682 e671.	Already included in review
Majid, I. (2013). Indian J Dermatol 58: 113-116.	Outcomes not relevant
Majid, I. (2019). DermatolTher: e12923.	Outcomes – not relevant
Malathi, M. (2013). Indian J Dermatol Venereol Leprol 79: 842-846.	Study design- review; non-systematic
Martinez-Cabriales, S. A., M. Bohdanowicz, et al. (2020). Dermatol Ther: e13233.	Case report

Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Nardin, C. (2019). Acta dermato-venereologica 99: 913-914	Case report
Parsad, D. (2003). Clin Exp Dermatol 28: 285-287.	Included in Whitton, Cochrane Database Syst 2015
Patel, I. K. (1993). Indian J Dermatol Venereol Leprol 59: 247-250.	Included in Whitton, Cochrane Database Syst 2015
Patra, S. (2019). J AmAcad Dermatol	Outcomes – not relevant
Radakovic-Fijan, S. (2001). J Am Acad Dermatol 44: 814-817.	Included in Matin, Clin Evid (Online) 2011
Radmanesh, M. (2006). J Dermatolog Treat 17: 151-153.	Included in Whitton, Cochrane Database Syst 2015
Rath, N. (2008). Indian J Dermatol Venereol Leprol 74: 357-360.	Included in Whitton, Cochrane Database Syst 2015
Rigopoulos, D. (2007) Dermatol	Outcomes – not relevant
Siadat, A. H. (2014). Dermatol Res Pract 2014: 240856.	Outcomes- reporting of VIDA score; no extractable data.
Taneja, A., A. Kumari, et al. (2019). Indian J Dermatol Venereol Leprol 85(5): 528-531.	Outcome; percentage repigmentation not repoted
Vanderweil, S. G. (2017). J Am Acad Dermatol 76: 150-151 e153.	Outcomes – not relevant
Vasistha, L. K. (1979). Indian J Med Res 69: 308-311.	Outcomes – not relevant
Wakkee, M. (2008). J Am Acad Dermatol 59: S57-58.	Case report
Watabe, A. (2018). J Dermatol 45: 456-462.	Outcomes – not relevant
Wendling, D. (2014). Expert Rev Clin Immunol 10: 159-169.	Study design - review; not a systematic review
xmd7x, R. B. R. (2018). Http://www.who.int/trialsearch/trial2.aspx?Trialid=rbr-6xmd7x.	Clinical trial; unpublished data
Zohdy, H. A.-E.-W. (2019). J Cosmet Dermatol 18: 1430-1434.	Outcomes – not relevant
Zohdy, H. A.-E.-W. (2018). Journal of cosmetic dermatology.	Duplicate; superseded by Zohdy, H. A.-E.-W. (2019). J Cosmet Dermatol 18: 1430-1434.

Light and laser therapies

Reference	Reason for exclusion
Abd El-Samad, Z. (2012). J Dermatolog Treat 23: 443-448.	Within-patient study (See Appendix G)
Abdel Latif, A. A. (2015). Dermatol Ther 28: 383-389.	Within-patient study (See Appendix G)
Abdel Sabour Makki, M., W. Saudi, et al. (2019). Journal of the Egyptian Women's Dermatologic Society 16(3): 179-183	Within-patient study (See Appendix G)
Abdullah, S. A. and M. Y. Saeed (2019). International Journal of Pharmaceutical Research 11(3): 1090-1097.	Within-patient study; not available

Reference	Reason for exclusion
Ada, S. (2005). Photodermatol Photoimmunol Photomed 21: 79-83.	Outcomes – response to treatment (repigmentation) was not reported for the individual interventions.
Akdeniz, N. (2014). J Dermatolog Treat 25: 196-199.	Included in Whitton, Cochrane Database Syst Rev 2015
Ameen, M. (2001). Br J Dermatol 145: 476-479.	Study design – variation in follow-up period and a large difference in the group sizes.
Anbar, T. (2017). DermatolTher30(1).	Outcomes – not relevant
Anbar, T. S. (2008). Photodermatol Photoimmunol Photomed 24: 322-329.	Included in Whitton, Cochrane Database Syst Rev 2015
Asawanonda, P. (2008). Acta Derm Venereol 88: 376-381.	Included in Whitton, Cochrane Database Syst Rev 2015
Asawanonda, P. (2010). Photomed Laser Surg 28: 679-684.	Included in Whitton, Cochrane Database Syst Rev 2015
Ayob, S. (2018). Journal of the European Academy of Dermatology and Venereology 32: e307-e308.	Letter (lack of information)
Babino, G. (2016). Photomed Laser Surg 34: 200-204.	Not available
Bae, J. M. (2016). J Am Acad Dermatol 74: 907-915.	Already included in first top-up
Bae, J. M. (2019). Lasers in surgery and medicine 51: 239-244.	Within-patient study (See Appendix G)
Bae, J. M. (2019). Pigment Cell Melanoma Res 32: 714 - 718	Outcomes; sufficient higher quality evidence
Bakis-Petsoglou, S. (2009). Br J Dermatol 161: 910-917.	Included in Whitton, Cochrane Database Syst Rev 2015
Bansal, S. (2013). Photodermatol Photoimmunol Photomed 29: 311-317.	Included in Whitton, Cochrane Database Syst Rev 2015
Batchelor, J., P. Akram, et al. (2019). Br J Dermatol 181(S1): 9-14.	Conference abstract
Baysal, V. (2003). J Eur Acad Dermatol Venereol 17: 299-302.	Outcomes – response to treatment (repigmentation) was reported only for lesion site and not for the individual interventions.
Bhatnagar, A. (2007). J Eur Acad Dermatol Venereol 21: 638-42.	Included in Whitton, Cochrane Database Syst Rev 2015; Xiao, B.-H. JDermatolog Treat 2015
Cabrera, R. (2018). Acta dermato-venereologica 98: 416 - 420.	Sufficient higher quality evidence available
Chahar, Y. S. (2018). Indian journal of dermatology 63: 399-402.	Sufficient higher quality evidence available
Casacci, M. (2007). J Eur Acad Dermatol Venereol 21: 956-963.	Included in Whitton, Cochrane Database Syst Rev 2015; Xiao, B.-H. J Dermatolog Treat 2015
Cherif, F. (2003). Dermatol Online J 9: 4.	Within-patient study (See Appendix G)
ChiCtr (2018). Http://www.who.int/trialsearch/trial2.aspx?Trialid=chictr1800014362.	Clinical trial; unpublished data
Chiu, S.-H. (2018). Journal of Dermatological Science 92: 218-220.	Letter (lack of information); intervention (some given systemic steroids and topical corticosteroids in addition)

Reference	Reason for exclusion
Cunha, P. (2017), Dermatologic therapy 30: no pagination.	Outcomes – not relevant
Dang, Y. P. (2016). Dermatol Ther 29: 126-133.	Systematic review - Exclude as indirect comparisons were made and there were problems with the methods of analysis.
Dayal, S. (2016). Pediatr Dermatol 33: 646-651.	Within-patient study (See Appendix G)
Dell'Anna, M. L. (2007). Clin Exp Dermatol 32: 631-636.	Included in Whitton, Cochrane Database Syst Rev 2015
Dong, D.-K. (2017). Pediatr Dermatol 34: 266-270.	Sufficient higher quality evidence available
Doghaim, N. N. (2019). Journal of Cosmetic Dermatology 18: 142-149.	Within-patient study (See Appendix G)
Doghaim, N. N., R. A. El-Tatawy, et al. (2020). J Cosmet Dermatol 19(1): 122-130.	Within-patient study (See Appendix G)
Eldelee, S. A., S. F. Gheida, et al. (2019). J Dermatolog Treat: 1-8.	Within-patient study (See Appendix G)
El Mofty, M. (2013). Clin Exp Dermatol 38: 830-835.	Included in Whitton, Cochrane Database Syst Rev 2015
El Mofty, M. (2016). Dermatol Ther 29: 406-412.	Outcomes – not relevant
Eleftheriadou, V. (2016). ClinDermatol 34: 603-606.	Study design; outcomes
El-Mofty, M. (2013). Photodermatol Photoimmunol Photomed 29: 239-246.	Included in Whitton, Cochrane Database Syst Rev 2015; Xiao, B.-H. J Dermatolog Treat 2015
El-Zawahry, B. M. (2012). Photodermatol Photoimmunol Photomed 28: 84-90.	Included in Whitton, Cochrane Database Syst Rev 2015; Xiao, B.-H. J Dermatolog Treat 2015
El-Zawahry, M. B. (2017). Lasers Med Sci 32: 1953-1958.	Unable to obtain full text
El-Zawahry, B. M. (2018). Journal of cosmetic dermatology 28: 84-90	Outcomes
Esfandiarpour, I. (2009). J Dermatolog Treat 20: 14-18.	Included in Whitton, Cochrane Database Syst Rev 2015
Esmat, S. (2016). Clin Dermatol 34: 594-602.	Study design; outcomes
Esmat, S. (2017). Dermatologic clinics 35: 171-192.	Study design – review; not systematic
Esme, P., G. Gur Aksoy, et al. (2019). Dermatol Surg 45(12): 1627-1634.	Within-patient study (See Appendix G)
Fa, Y. (2017). J Eur Acad Dermatol Venereol 31: 337-340.	Sufficient higher quality evidence available
Fenniche, S. (2018). Dermatol Ther 8: 127-135.	Sufficient higher quality evidence available
Gamil, H. (2010). Clin Exp Dermatol 35: 919-921.	Outcomes – reporting VIDA score; outcome does not match protocol
Ghasemloo, S. (2019). J Dermatolog Treat 30: 697-700.	Within-patient study (See Appendix G)
Goktas, E. O. (2006). J Eur Acad Dermatol Venereol 20: 553-557.	Within-patient study (See Appendix G)

Reference	Reason for exclusion
Hamzavi, I. (2004). Arch Dermatol 140: 677-683.	Included in Whitton, Cochrane Database Syst Rev 2015
Hartmann, A. (2005). Int J Dermatol 44: 736-742.	Population; n <10
Hartmann, A. (2014). Eur J Dermatol 24: 551-559.	Study design – the number of treatment sessions and follow-up varied amongst the groups
Hirobe, T. (2019). International journal of dermatology 58: 210-217.	Outcomes
Huang, C., P. Li, et al. (2020). Lasers Surg Med. 52: 590 - 596	Sufficient higher-quality evidence available
Hui-Lan, Y. (2009). Pediatr Dermatol 26: 354-356.	Included in Whitton, Cochrane Database Syst Rev 2015; Bae J Am Acad Dermatol, 2016
Ibrahim, H. (2018). J CosmetDermatol. 17: 911-916	Outcomes – not relevant
Ibrahim, Z. A. (2016). J Cosmet Dermatol 15: 108-116	Within-patient study (See Appendix G)
Jorge, M.-T., O.-S. J. María, et al. (2020). Actas Dermo-Sifiliográficas (English Edition) 111: 41 - 46	Study design and outcomes; response has not been defined by the % of repigmentation achieved
Jprn, U. (2018). Http://www.who.int/trialsearch/trial2.aspx?Trialid=jprn-umin000032165.	Clinical trial; unpublished data
Kadry, M. (2018). Clinical, cosmetic and investigational dermatology 11: 551-559.	Within-patient study (See Appendix G)
Kanokrungsee, S. (2016). Lasers Med Sci 31: 1343-1349.	Intervention; includes broad band UVB
Khalid, M. (1995). Int J Dermatol 34: 203-205.	Included in Whitton, Cochrane Database Syst Rev 2015
Khandpur, S. (2018). Indian J Dermatol Venereol Leprol 84: 78-80.	Outcomes; study design
Khullar, G. (2015). J Eur Acad Dermatol Venereol 29: 925-932.	Within-patient study (See Appendix G)
Klahan, S. (2009). Clin Exp Dermatol 34: e1029-1030.	Included in Whitton, Cochrane Database Syst Rev 2015
Kullavanijaya, P. (2004). Photodermatol Photoimmunol Photomed 20: 248-251.	Within-patient study (See Appendix G)
Le Duff, F. (2010). Br J Dermatol 163: 188-192.	Included in Whitton, Cochrane Database Syst Rev 2015; Sun, Y. J Dermatolog Treat 2015
Lee, H. (2017). J Eur Acad Dermatol Venereol 31: 894-897.	Study design; Outcomes
Lee, J. (2016). Dermatol 232: 224-229.	Sufficient higher quality evidence available
Leone, G. (2015). G Ital Dermatol Venereol 150: 461-466.	Outcomes; no extractable data
Li, J. Y. (2014) J Clin Dermatol: 115-7	Foreign language
Li, L., Q. Ma, et al. (2019). J Int Med Res 47(11): 5623-5631.	Outcome

Reference	Reason for exclusion
Linthorst Homan, M. W. (2012). J Eur Acad Dermatol Venereol 26: 690-695.	Included in Whitton, Cochrane Database Syst Rev 2015; Sun, Y. J Dermatolog Treat 2015; Xiao, B.-H. J Dermatolog Treat 2015
Lommerts, J. (2017), Br J Dermatol 177: 1293 - 1298	Population (includes patients with piebaldism, only 3 patients with segmental vitiligo are included)
Lommerts, J. E. (2017). Br J Dermatol 177: e60-e61.	Study design; outcomes
Lotti, T. (2018). Open Access Maced J Med Sci 6: 43-45.	Sufficient higher quality evidence available
Lotti, T. (2018). Open Access Maced J Med Sci 6: 49-51.	Sufficient higher quality evidence available
McKesey, J. and A. G. Pandya (2019). J Am Acad Dermatol 81(2): 646-648.	Study design; letter, lack of information reported
Mehta, C., T. Mohammad, et al. (2019). Photodermatol Photoimmunol Photomed 35(5): 318-321.	Pilot study; population, n = 4
Middelkamp-Hup, M. A. (2007). J Eur Acad Dermatol Venereol 21: 942-950.	Included in Whitton, Cochrane Database Syst Rev 2015
Mohaghegh, F. (2012) J Res Med Sci, 17: S131-S3	Included in Whitton, Cochrane Database Syst Rev 2015
Mohammad, T. F. (2017). J Am Acad Dermatol 76: 879-888.	Study design
Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Nahidi, Y., P. Layegh, et al. (2019). Iranian Journal of Dermatology 22(1): 1-6.	Outcomes - looking at vitamin D3 levels following NB-UVB treatment
Nguyen, S. (2018). JAMA Dermatology 154: 725-726.	Outcomes (VASI); letter (lack of information reported)
Nisticò, S. (2012). Photomed Laser Surg 30: 26-30.	Included in Whitton, Cochrane Database Syst Rev 2015; Bae J Am Acad Dermatol, 2016
Oh, S. H. (2011). J Am Acad Dermatol 65: 428-430.	Included in Whitton, Cochrane Database Syst Rev 2015; Bae, J Am Acad Dermatol 2016
Orecchia, G. (1992). Dermatol 184: 120-123.	Within-patient study (See Appendix G)
Orecchia, G. (1998) J Dermatolog Treat, 9: 65-9	Within-patient study (See Appendix G)
Park, O. J. (2016). Clin Exp Dermatol 41: 236-241.	Outcomes – not relevant
Park, M. J., U. Shon, et al. (2019). Photodermatol Photoimmunol Photomed. 00: 1 -8	Within-patient study (See Appendix G)
Parsad, D. (1998). Dermatol197: 167-170.	Included in Whitton, Cochrane Database Syst Rev 2015
Passeron, T. (2004). Arch Dermatol 140: 1065-1069.	Included in Whitton, Cochrane Database Syst Rev 2015; Bae, J Am Acad Dermatol 2016
Pathak, M.A. (1984) Natl Cancer Inst Monogr, 66: 165-73	Unable to obtain full text
Procaccini, E.M. (1995) J Dermatolog Treat, 6: 117-20	Included in Whitton, Cochrane Database Syst Rev 2015

Reference	Reason for exclusion
Radmanesh, M. (2006). J Dermatolog Treat 17: 151-153.	Included in Whitton, Cochrane Database Syst Rev 2015
Raghuwanshi, A. D. (2018). Indian J Dermatol Venereol Leprol 84: 49-53.	Sufficient higher quality evidence available
Rajegowda, H. M., S. K. Basavapura Madegowda, et al. (2019). Journal of Pakistan Association of Dermatologists 29(4): 390-395.	Sufficient higher-quality evidence available
Rodríguez-Martín, M. (2009). Br J Dermatol 160: 409-414.	Included in Whitton, Cochrane Database Syst Rev 2015; Matin, R., Clin Evid (online) 2011
Sahu, P. (2016). Photodermatol Photoimmunol Photomed 32: 262-268.	Within-patient study (See Appendix G)
Salah Eldin, M. M. (2017). J Lasers Med Sci 8: 123-127.	Outcomes – not relevant
Salazar, G. Z. (2013), Med Cutan Ibero Lat Am 41: 205-209.	Foreign language
Sapam, R. (2012). Int J Dermatol 51: 1107-1115.	Included in Whitton, Cochrane Database Syst Rev 2015
Sassi, F. (2008). Br J Dermatol 159: 1186-1191.	Included in Whitton, Cochrane Database Syst Rev 2015; Bae, J Am Acad Dermatol 2016
Satyanarayan, H. S. (2013). Indian J Dermatol Venereol Leprol 79: 525-527.	Included in Whitton, Cochrane Database Syst Rev 2015
Sharma, S. (2018). J Eur Acad Dermatol Venereol 32: e330-e331.	Within-patient study (See Appendix G)
Shi, Q. (2013). Photodermatol Photoimmunol Photomed 29: 27-33.	Included in Whitton, Cochrane Database Syst Rev 2015; Sun, Y., J Dermatolog Treat 2015
Shin, J. (2012). Br J Dermatol 166: 658-661.	Included in Whitton, Cochrane Database Syst Rev 2015
Siadat, A. H. (2014). Dermatol Res Pract 2014: 240856.	Outcomes – not relevant
Silpa-Archa, N. (2019). J Dermatolog Treat 30: 691-696.	Sufficient higher-quality evidence available
Silpa-Archa, N., P. Weerasubpong, et al. (2019). J Dermatolog Treat 30: 691-696.	Duplicate
Soliman, M. (2016). J Cosmet Laser Ther 18: 7-11.	Within-patient study (See Appendix G)
Sung, J. M. (2018). Journal of the american academy of dermatology 78: 605-607.e601.	Outcomes; letter (lack of information reported)
Suwarsa, O., H. Gunawan, et al. (2019). Dermatology Reports 11: 81-83.	Outcomes (looking at 25-hydroxyvitamin D levels)
Tjioe, M. (2002). Acta Derm Venereol 82: 369-372.	Included in Whitton, Cochrane Database Syst Rev 2015
Thu, H. D. T. (2019). Open access Macedonian journal of medical sciences 7: 256-258.	Outcomes
Ullah, G. (2017). JP A D 27: 232-237.	Comparative study; no extractable data (See Appendix F)
Uitentuis, S. E. (2019). J Dermatolog Treat 30: 594-597.	Comparative study; no extractable data (See Appendix F)

Reference	Reason for exclusion
Uitentuis, S. E. (2019). J Dermatolog Treat 30: 594-597.	Duplicate
Valkova, S. (2004). Clin Exp Dermatol 29: 180-184.	Study design - pilot study, follow-up period varied between the two groups.
Verhaeghe, E. (2011). Dermatol 223: 343-348.	Included in Whitton, Cochrane Database Syst Rev 2015; Xiao, B.-H. J Dermatolog Treat 2015
Westerhof, W. (1997). Arch Dermatol 133: 1525-1528.	Comparative study; no extractable data (See Appendix F)
Westerhof, W. (1999). Arch Dermatol 135: 1061-1066.	Included in Whitton, Cochrane Database Syst Rev 2015
Yang, Y. S. (2010). Int J Dermatol 49: 317-323.	Included in Sun, Y. J, Dermatolog Treat 2015
Yazici, S. (2017). Turk J Med Sci 47: 381-384.	Sufficient higher quality evidence available
Yones, S. S. (2007). Arch Dermatol 143: 578-584 [Erratum: (2007) 2143: 2906].	Included in Whitton, Cochrane Database Syst Rev 2015
Yuan, J. (2016). Eur J Dermatol 26: 592-598.	Unable to obtain full text
Zabolinejad, N., M. Maleki, et al. (2020). Australas J Dermatol 61(1): e65-e69.	Outcomes (VASI)
Zhang, Y. (2013), Zhongguo zhen jiu [CAM]: 121-124.	Foreign language
Zhao, Y.-D. (2017), J Clin Dermatol 46: 310-312.	Unable to obtain full text

Combination therapies

Reference	Reason for exclusion
Akdeniz, N. (2014). J Dermatolog Treat 25: 196-199.	Included in Whitton, Cochrane Database Syst Rev 2015
Bakis-Petsoglou, S. (2009). Br J Dermatol 161: 910-917.	Included in Whitton, Cochrane Database Syst Rev 2015
Bapur Erduran, F. (2016). Photodermatol Photoimmunol Photomed 32: 247-253.	Outcomes – not relevant
Bayoumi, W. (2012). Br J Dermatol 166: 208-211.	Included in Whitton, Cochrane Database Syst Rev 2015
Chen, W. (2018). Lasers in Surgery and Medicine 50: 829-836.	Included in Arora 2020
Garg, S. (2019). Dermatologic Surgery 45: 83-89.	Sufficient higher quality evidence
Giorgio, C. M. (2019). Dermatol Surg 45: 1424 – 1426	Not available
Fai, D. (2007). J Eur Acad Dermatol Venereol 21: 916-920.	Within-patient study (See Appendix G)
Fai, D. (2017). Giornale Italiano di Dermatologia e Venereologia 152: 402-404.	Unable to obtain full text
Gawkrodger, D. J. (2008). Br J Dermatol 159: 1051-1076.	Study design; guideline
Giorgio, C. M. (2019). Dermatologic surgery: official publication for American	Unable to obtain full text

Reference	Reason for exclusion
Society for Dermatologic Surgery [et al.]. 45: 1424 - 1426	
Hirobe, T. (2018). Dermatologica Sinica 36: 203-206.	Case report
Ibrahim, Z. A. (2019). JCosmetDermatol18: 581-588.	Within-patient study (See Appendix G)
Iwanowski, T. (2018). Postepy dermatologii i alergologii 35: 592-598.	Case report (10 cases)
Jha, A. K. (2019). JAm Acad Dermatol 80(4): e75-e76.	Case report
Joshipura, D. (2018). J Dermatol Treat 29: 98-99.	Unable to obtain full text
Jowkar, F. (2019). The Journal of dermatological treatment: 1-5.	Not available
Jung, H. M. (2018). J Am Acad Dermatol	Not available
Kadry, M. (2018). Clinical, cosmetic and investigational dermatology 11: 551-559.	Within-patient study (See Appendix G)
Kim, S. A. (2015). J Eur Acad Dermatol Venereol 29: 713-718.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**)
Kim, S. R. (2018). JAMA Dermatol 154: 370-371.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Khan, R. (2018). Australasian Journal of Dermatology 59: e315-e318.	Sufficient higher quality evidence
Korobko, I. V. (2016). Dermatol Ther 29: 437-441.	Within-patient study (See Appendix G)
Kwon, H. B. (2013). J Drugs Dermatol 12: e63-67.	Unable to obtain full text
Kumar, A. (2019). J Am Acad Dermatol 81: e67-e69.	Case report
Lagrange, S. (2019). British Journal of Dermatology. 180: 1539 - 1540	Letter (lack of information reported)
Lee, J. (2016) Dermatol 232: 224-9	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Li, L. (2015). Dermatol Ther 28: 131-134.	Within-patient study (See Appendix G)
Liu, L., Y. Wu, et al. (2019). J Dermatolog Treat 30(4): 320-327.	Within-patient study (See Appendix G)
Liu, L., Y. Wu, et al. (2019). J Dermatolog Treat 30(4): 320-327.	Duplicate
Majid, I. (2009) Indian J Dermatol 54:124-7	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
McKesey, J. (2019). Journal of the American Academy of Dermatology. 81: 646 - 648	Letter (lack of information reported)
Mina, M. (2018). J Cosmet Dermatol 17: 744-751.	Within-patient study (See Appendix G)

Reference	Reason for exclusion
Mina, M. (2018). Journal of cosmetic dermatology 17: 744-751.	Duplicate
Mokhtari, F. (2018). J Cosmet Dermatol 17: 165-170.	Outcomes – not relevant
Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Namazi, M. R. (2015). Iran J Med Sci 40: 478-484.	Outcomes - VASI score reported
Nisticò, S. (2012). Photomed Laser Surg 30: 26-30.	Included in Whitton, Cochrane Database Syst Rev 2015
Nordal, E. J. (2011). J Eur Acad Dermatol Venereol 25: 1440-1443.	Included in Whitton, Cochrane Database Syst Rev 2015
Oh, S. H. (2011). J Am Acad Dermatol 65: 428-430.	Included in Whitton, Cochrane Database Syst Rev 2015
Oiso, N. (2013). J Dermatol 40: 344-354.	Study design; guideline
Shafiee, A. (2018). Phytother Res32: 1812-1817.	Outcomes – percentage of repigmentation not reported
Shih, S. (2019). Dermatologic Therapy 32: e12773	Letter; review narrative
Shivasaraun, U. V. (2018). MedHypotheses 121: 26-30.	Study design; outcomes
Stanimirovic, A. (2016). Dermatol Ther 29: 312-316.	Outcomes – not relevant
Suwarsa, O., H. Gunawan, et al. (2019). Dermatology Reports 11(S1): 65-67.	Outcomes (looking at serum 25-(OH)D levels)
Taieb, A. (2013). Br J Dermatol 168: 5-19.	Study design; guideline
Tsuchiyama, K. (2016). Dermatol 232: 237-241.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**)
Tovar-Garza, A. (2019). Br J Dermatol 180: 193-194.	Outocmes; repigmentation doesn't reach 50% threshold
Toh, J. J. H., S. Y. Chuah, et al. (2020). 82: 1517 - 1519	Outcomes
Urso, B. (2017). Dermatol Ther 30.	Outcomes -not relevant
Vachiramon, V. (2016). Lasers Surg Med 48: 197-202.	Within-patient study (See Appendix G)
Wen, X. (2019). Dermatologic Therapy 32: e12747	Within-patient study (See Appendix G)
Wu, Y. (2019). Br J Dermatol. 181: 210 – 1	letter, lack of information
Yan, R. (2017). Lasers Med Sci 32: 1571-1577.	Intervention; only comparing low, medium, and high energy Er:YAG laser
Zhang, Y. (2018). Anais brasileiros de dermatologia 93: 539-545.	Case reports; n=3

Surgical therapies

Reference	Reason for exclusion

Altalhab, S., M. I. AlJasser, et al. (2019). J Eur Acad Dermatol Venereol 33(6): 1172-1176.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Altalhab, S., M. I. AlJasser, et al. (2019). J Eur Acad Dermatol Venereol 33(6): 1172-1176.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Attwa, E. M., S. A. Khashaba, et al. (2020). J Cosmet Dermatol 19: 1473 - 1478	Within-patient study (See Appendix G)
Awad, S. S. (2016). J CosmetDermatol 15: 383-386.	Outcomes – not relevant
Bae, J. M. (2018). Journal of the American Academy of Dermatology 79: 720-727.e721.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Bao, H. (2015). J Dermatolog Treat 26: 571-574.	Within-patient study (See Appendix G)
Bassiouny, D. (2018). Clinical, cosmetic and investigational dermatology 11: 521-540.	Study design; outcomes
Benzekri, L. (2017). Pigment Cell Melanoma Res 30: 493-497.	Study design; outcomes
Budania, A. (2014). Br J Dermatol 171: 154.	Included in Whitton, Cochrane Database Syst 2015
Chatterjee, M. (2016). J Cutan Aesthet Surg 9: 97-100.	Outcomes – not relevant
Dellatorre, G. (2017). Anais brasileiros de dermatologia 92: 888-890.	Study design; outcomes
Dillon, A. B. (2017). J Clin Aesthet Dermatol 10: 15-28.	Outcomes; study design
Ding, X., M. Zhao, et al. (2019). J Dermatolog Treat: 1-5.	Outcomes (repigmentation not defined)
Donaparthi, N. (2016). Indian J Dermatol 61: 640-644.	Within-patient study (See Appendix G)
Ebadi, A. (2015) J Eur Acad Dermatol Venereol 29: 745-51	Within-patient study (See Appendix G)
El-Zawahry, B. M. (2017). Dermatol Surg 43: 226-235.	Unable to obtain full text
Ezz-Eldawla, R. (2018). The Journal of dermatological treatment: 1-6.	Superseeded by Ezz-Eldawala 2019
Feily, A. (2016). Dermatol Surg 42: 1082-1088.	Unable to obtain full text
Gan, E. Y. (2016). J Am Acad Dermatol 75(3): 564-571.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Gill, B. S., M. S. Brar, et al. (2019). J Family Med Prim Care 8(9): 2912-2916.	Outcomes; repigmentation percentage does not meet threshold
Gupta, S. (2018). Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al.] 44: 895-896.	Study design
Gupta, S. (2019). Indian Journal of Dermatology, Venerology and Leprology 85: 32 – 38	Outcomes (<50% repigmentation)

Hirobe, T. (2018). Dermatologica Sinica 36: 203-206.	Outcomes – not relevant
Janowska, A. (2016). Int Wound J 13 Suppl 3: 47-51.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Jin, Y. (2011) Cutis 87: 137-41.	Methadology unclear; outcomes
Kachhawa, D. (2017). J Cutan Aesthet Surg 10: 81-85.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Khandpur, S. (2005) Dermatol Surg, 31: 436-41.	Included in Whitton, Cochrane Database Syst 2015
Komen, L. (2017). Journal DermatolTreat 28: 86-91.	Within-patient study (See Appendix G)
Kumar, P. (2018). Int J Dermatol 57: 245-249.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Kumar, A., R. Bharti, et al. (2019). J Am Acad Dermatol 81(3): e67-e69.	Case report
Lee, S. H. (2019). Dermatologic Surgery 45: 300-303.	Case report
Lee, D. Y. (2009). Clin Exp Dermatol 34: 838.	Case report
Lee, K. J. (2007). Dermatol Surg 33: 1002-1003.	Case report
Lee, S. H. (2019). Dermatologic Surgery 45: 300-303.	Case report
Li, J. (2019). Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.] 45: 497-505.	Not available
Liu, B. (2019). The Journal of dermatological treatment: 1-19.	Not available; ahead of print
Lommerts, J. (2017), Br J Dermatol 177: 1293 - 1298	Population (includes patients with piebaldism, only 3 patients with segmental vitiligo are included)
Majid, I. (2017). Dermatol Surg 43: 218-225.	Unable to obtain full text
Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Mrigpuri, S. (2019). Journal of the European Academy of Dermatology and Venereology: JEADV 33: 185-190.	Within-patient study (See Appendix G)
Muhammed, R. T. (2018). JAMA dermatology 154: 301-308.	Within-patient study (See Appendix G)
Njoo, M. D. (1998). Arch Dermatol 134: 1543-1549.	Outcomes – not relevant
Oh, S. J., C. R. Kim, et al. (2019). Annals of Dermatology 31(6): 687-689.	Letter (lack of information reported)
Orouji, Z. (2018). J Dermatol Sci 89: 52-59.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Ozdemir, M. (2002). Int J Dermatol 41: 135-138.	Included in Whitton, Cochrane Database Syst 2015

Pangti, R., A. Challa, et al. (2020). Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.].	Within-patient study; not available
Parambath, N. (2019). International Journal of Dermatology 58: 472-476.	Within-patient study (See Appendix G)
Ramos, M. G. (2017). An Bras Dermatol 92: 312-318.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Rasheed, H. M., S. M. Esmat, et al. (2020). Dermatol Surg.	Within-patient study; not available
Razmi, T. M. (2018). JAMA Dermatol 154: 301-308.	Within-patient study (See Appendix G)
Sahni, K. (2011). Dermatol Surg 37: 176-182	Included in Whitton, Cochrane Database Syst 2015
Shashikiran, A. R. (2018). Indian Journal of Dermatology, Venereology and Leprology 84: 203-205.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Shi, H. X., R. Z. Zhang, et al. (2019). Indian J Dermatol Venereol Leprol. 86: 124 - 133	Study design
Silpa-Archa, N. (2016), Br J Dermaotol 174: 895-897.	Study design (preliminary study)
Silpa-Archa, N. (2017). J Am Acad Dermatol 77: 318-327.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Singh, C. (2013). Br J Dermatol 169: 287-293.	Included in Whitton, Cochrane Database Syst 2015
Subramaniyan, R. (2019). Journal of the American Academy of Dermatology.	Case reports (n = 4)
Tawfik, Y. M. (2019). Journal of Cosmetic Dermatology 18: 638-646.	Within-patient study (Appendix G**: Narrative findings from within-patient studies**)
Tovar-Garza, A. (2019). J Am Acad Dermatol 80: 1152-1154.	Retrospective case series letter (lack of information)
Tsuchiyama, K. (2016). Dermatol 232: 237-241.	In previous search
Vakharia, P. P. (2018). International Journal of Dermatology 57: 770-775.	Review; not systematic
van Geel, N. (2004). Arch Dermatol 140: 1203-1208.	Included in Whitton, Cochrane Database Syst 2015
van Geel, N. (2010). Br J Dermatol 163: 1186-1193.	Unable to obtain full text
Xu H, L. R., Liu Y, Lu T (2017), Journal of clinical dermatology 46: 447-449.	Unable to obtain full text
Zanardelli, M. (2016). Giornale italiano di dermatologia e venereologia 151: 726-727.	Unable to obtain full text
Zhang, D. M. (2014). Dermatol Surg 40: 420-426.	Unable to obtain full text

Psychological therapies

Reference	Reason for exclusion
Aghaei, S. (2004). BMC Dermatol 4: 8.	Study design- not assessing the effect of a psychological intervention on vitiligo patients
Ahmed, A. (2018). Journal of the European Academy of Dermatology and Venereology: JEADV 32: 2275-2283.	Study design; outcomes
Al Robaee, A. A. (2007). Saudi Med J 28: 1414-1417.	Study design- not assessing the effect of a psychological intervention on vitiligo patients
AlGhamdi, K. M. (2010). Int J Dermatol 49: 1141-1145.	Study design- not assessing the effect of a psychological intervention on vitiligo patients
Al-Harbi, M. (2013). Skinmed 11: 327-330.	Study design- not assessing the effect of a psychological intervention on vitiligo patients
Ali, M. A. S. (2016). Dermatologic Therapy 29: 413-418.	Study design, outcomes not relevant
Amer, A. A. (2015). Acta Derm Venereol 95: 322-325.	Population- investigating the mental health and QoL of parents whose children have vitiligo
Anbar, T. S. (2014). Exp Dermatol 23: 219-223.	Study design- review (non-systematic)
Augustin, M. (2008). Dermatology 217: 101-106.	Study design- not assessing the effect of a psychological intervention on vitiligo patients
Balaban, O. z. D. (2011). Dusunen Adam 24: 306-313.	Study design- not assessing the effect of a psychological intervention on vitiligo patients
Bhandarkar, S. S. (2012). Dermatol Clin 30: 255-268, viii.	Study design – review; not systematic
Bilgiç, O. (2011). Clin Exp Dermatol 36: 360-365.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Bonotis, K. (2016). J Dtsch Dermatol Ges 14: 45-49.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Chan, M. F. (2012). J Clin Nurs 21: 1614-1621.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Chan, M. F. (2013). Int J Nurs Pract 19 Suppl 3: 3-10.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Choi, S. (2010). J Eur Acad Dermatol Venereol 24: 524-529.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Connor, C. J. (2017). Clinical, Cosmetic and Investigational Dermatol 10: 117-132.	Study design; outcomes
Dolatshahi, M. (2008). Indian J Dermatol Venereol Leprol 74: 700.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Doɬruk Kaçar, S. (2014). Turkiye Klinikleri Dermatoloji 24: 45-50.	Unable to obtain full text
Fawzy, M. M. (2013). Eur J Dermatol 23: 733-734.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Ghaderi, R. (2014). Shiraz E Med J 15.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Gupta, V. (2014). Br J Dermatol 171: 1084-1090.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Hamidizadeh, N., S. Ranjbar, et al. (2020). Health Qual Life Outcomes 18: 20.	Study design (epidemiological); outcomes

Reference	Reason for exclusion
Jha, A. (2016). Indian J DermatolVenereol Leprol82: 308-310.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**)
Kent, G. (1996). Clin Exp Dermatol 21: 330-333.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Kent, G. (1996). J Am Acad Dermatol 35: 895-898.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Kent, G. (1999). Psychol Health 14: 241-251.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Krishna, G. S. (2013). Indian J Dermatol Venereol Leprol 79: 205-210.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Krüger, C. (2013). Curr Probl Dermatol 44: 102-117.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Krüger, C. (2015). Acta Derm Venereol 95: 553-558.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Mattoo, S. K. (2002). J Eur Acad Dermatol Venereol 16: 573-578.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Nogueira, L. S. (2009). An Bras Dermatol 84: 41-45.	Study design- not assessing the effect of a psychological intervention on vitiligo patients.
Ongenae, K. (2005). Br J Dermatol 152: 1165-1172.	Study design- not assessing the impact of a psychological intervention on vitiligo patients. The study also includes patients with psoriasis.
Önen, Ö., S. Kundak, et al. (2018). Psychiatry and Clinical Psychopharmacology 29(4): 492-501.	Study design; outcomes
Owoeye, O. A. (2007). Int J Psychiatry Med 37: 129-138.	Population- patients with a variety of dermatological problems and not only vitiligo.
Pahwa, P. (2013). Indian J Dermatol Venereol Leprol 79: 679-685.	Study design- qualitative study not assessing the impact of a psychological intervention on vitiligo patients.
Papadopoulos, L. (1999). Br J Med Psychol 72: 385-396.	Comparative study, no extractable data (See Appendix F)
Papadopoulos, L. (2004). Dermatol Psychosom 5: 172-177.	Comparative study, no extractable data (See Appendix F)
Parsad, D. (2003). Br J Dermatol 148: 373-374.	Population- a patient with an unusual variant of granulomatous adnexotropic cutaneous T-cell lymphoma.
Radtke, M. A. (2009). Br J Dermatol 161: 134-139.	Study design- qualitative study not assessing the impact of a psychological intervention on vitiligo patients.
Radtke, M. A. (2010). Dermatol 220: 194-200.	Study design- not assessing the impact of a psychological intervention on vitiligo patients. The study also includes patients with psoriasis.
Rodriguez-Vallecillo, E. (2014). Psychiatr Clin North Am 37: 625-651.	Review; not systematic
Rzepecki, A. K. (2018). Journal of drugs in dermatology : JDD 17: 688-691.	Not available
Salzes, C. (2016). J Invest Dermatol 136: 52-58.	Study design- development and validation of a vitiligo burden assessment tool

Reference	Reason for exclusion
Sampogna, F. (2004). Psychosom Med 66: 620-624.	Population- Patients with a variety of dermatological problems and not only vitiligo.
Sampogna, F. (2008). Br J Dermatol 159: 351-359.	Study design- not assessing the impact of a psychological intervention on vitiligo patients. The study also includes patients with psoriasis.
Sampogna, F. (2013). G Ital Dermatol Venereol 148: 255-261.	Population- Patients with a variety of dermatological problems and not only vitiligo.
Sangma, L. N. (2015). Indian J Dermatol 60: 142-146.	Study design- not assessing the impact of a psychological intervention on vitiligo patients. The study also includes patients with psoriasis.
Sarhan, D. (2016). J Sex Marital Ther 42: 267-276.	Study design-focus on female genital self-image, sexual dysfunction and QoL in women with vitiligo.
Schwartz, R. (2009). Rev Med Chile 137: 53-62.	Foreign language
Şenol, A. (2013). Dermatol 226: 185-190.	Study design- study aimed to develop a QoL scale for vitiligo.
Shah, R. (2014). Br J Dermatol 171: 332-337.	Comparative study, no extractable data (See Appendix F)
Sharma, N. (2001). J Dermatol 28: 419-423.	Study design- not assessing the impact of a psychological intervention on vitiligo patients. The study also includes patients with psoriasis.
Shenefelt, P. D. (2014). Psychol Res Behav Manag 7: 201-212.	Study design- not assessing the impact of a psychological intervention on vitiligo patients. The study is focused on the spiritual and religious aspects of skin and skin disorders.
Shenoi, S. D. (2013). Clin Dermatol 31: 62-65.	Study design- review (non-systematic) of the role of cultural factors in the biophysical model of psychosomatic skin disease.
Speeckaert, R. (2016). J Invest Dermatol 136: 6-7.	Study design - commentary
Taïeb, A. (2018). Journal of the European Academy of Dermatology and Venereology 32: 2053-2054.	letter (lack of information reported); review, not systematic
Thompson, A. R. (2002). Br J Health Psychol 7: 213-225.	Study design- qualitative study assessing the experiences of living with vitiligo among white female vitiligo patients.
Wang, G. (2017). J Eur Acad Dermatol Venereol.	Unable to obtain full text
Watabe, A. (2018). J Dermatol 45: 456-462.	Outcomes – not relevant
Zabetian, S. (2017). J Drugs Dermatol 16: 344-350.	Unable to obtain full text

Skin camouflage therapies

Reference	Reason for exclusion
Akakpo, A. S. (2016). Ann Dermatol Venereol 143: 197-201.	Population – not specific to vitiligo

Chen, D. (2019). PloS one 14: e0210581.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Fenton, J. S. (2008). J Drugs Dermatol 7: 705-711.	Unable to obtain full text
Hsu, S. (2008). Dermatol Online J 14: 23.	Case report
Ongenae, K. (2005). Dermatol 210: 279-285	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Nct (2019). "Effects of Combination Therapy With Camouflage in the Repigmentation of Vitiligo." https://clinicaltrials.gov/show/NCT03973073.	Study record of clinical trial
Padilla-España, L. (2014) Actas Dermosifiliogr 105: 510-4	Prospective case series (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**)
Rajatanavin, N. (2008). Int J Dermatol 47: 402-406.	Prospective and retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Tanioka, M. (2010). J Cosmet Dermatol 9: 72-75.	Comparative study; no extractable data (See Appendix F)

Complementary therapies

Reference	Reason for exclusion
Cohen, B. E. (2015). Am J Clin Dermatol 16: 463-474.	Study design- review; not systematic
Colucci, R. (2015). Dermatol Ther 28: 17-21.	Outcomes- threshold for repigmentation does not match the protocol
Colucci, R., R. Conti, et al. (2019). International journal for vitamin and nutrition research 90: 200-204	Not available
Conforti, F. (2009). Curr Drug Ther 4: 38-58.	Study design – review; not systematic
Czarnowicki, T. (2011). J Eur Acad Dermatol Venereol 25: 959-963.	Retrospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Dhanik, A. (2011). Ayu 32: 66-69.	Outcomes – not relevant
Di Nardo, V. (2018). Dermatologic therapy: e12625.	Review; not systematic
Ediriweera, E. (2009), Ayu 30: 225-231.	Outcomes – not relevant
Felsten, L. M. (2011). J Am Acad Dermatol 65: 493-514.	Outcomes; study design – review; not systematic
Ghorbanibirgani, A. (2014). Iran Red Crescent Med J 16: e4515.	Outcomes- VASI score reported; no extractable data
Gianfaldoni, S. (2018). Open Access Macedonian Journal of Medical Sciences 6: 203-207.	Study design – review; not systematic
Grimes, P. E. (2017). Dermatologic Clinics 35: 235-243.	Study design – review; not systematic

Hassan, I. (2013; (100-1)) Indian J Dermatol Venereol Leprol	Outcomes – not relevant
Hemanta Kumar, P. (2012). Int J Res Ayurveda Pharm 3: 868-871.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**)
Jain, V. C. (2016). International Journal of Pharmaceutical Research 8: 76-79.	Unable to obtain full text
Korobko, I. V. (2014). Dermatol Ther 27: 219-222.	Outcomes – not relevant
Lopes, C. A. C. (2011). J Plast Dermatol 7: 5-10.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Mahesh, S. (2017). Am J Case Rep 18: 1276-1283.	Outcomes – not relevant
Mihăilă, B. (2019). Experimental and therapeutic medicine 17: 1039-1044.	Study design; outcomes
Morrison, B. (2017). Br J Dermatol 177: e338-e339.	Outcomes – not relevant
Rafeeqi, T. A., F. Jabeen, et al. (2019). J Complement Integr Med.	Study design; outcomes
Richmond, J. M. (2018). Science translational medicine 10.	Mouse study
Sarac, G. (2019). Dermatologic therapy: e12949.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Shraddhamayananda, S. (2012). Asian J Pharm Clin Res 5: 33-35.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studies**)
Szczurko, O. (2011) BMC Complement Altern Med 11:21	Outcomes – percentage depigmentation not defined
Van, T. N., T. T. Minh, et al. (2019). Open Access Maced J Med Sci 7(2): 283-286.	Duplicate
Vinodini, R., A. M. Amala Hazel, et al. (2019). Research Journal of Pharmacy and Technology 12(12): 5932-5936.	Within-patient study; not available
Watabe, A. (2018). J Dermatol 45: 456-462.	Outcomes
Widhiati, S., I. Julianto, et al. (2019). Dermatology Reports 11(S1): 11-13.	Prospective case series (See Appendix H**: Narrative findings from non-comparative studiesAppendix H: PRISMA diagram - study selection**)
Zhao, Y. (2016), Henan traditional chinese medicine [he nan zhong yi] 35: 1382-1384.	Unable to obtain full text

Appendix K: Methodology

Developing the review questions and outcomes

Review questions were developed using the PICO framework (patient, intervention, comparison and outcome) for intervention reviews. The use of this framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the technical team and refined and validated by the GDG. The questions were based on the key clinical areas.

A total of eleven systematic review questions were identified (see Appendix A).

Full literature searches, critical appraisals and evidence reviews were completed for ten of the review questions.

Searching for evidence

Clinical literature search

Systematic literature searches were undertaken to identify the published clinical evidence relevant to the review questions; these were undertaken according to the parameters stipulated within the protocols. Databases were searched using relevant medical subject headings (MeSH), free-text terms and study-type filters, where appropriate. Where possible, searches were restricted to articles published in English language; studies published in languages other than English were not reviewed. All searches were conducted in PubMed, MEDLINE, EMBASE and Cochrane databases to identify key articles relevant to the questions. All searches for this version were completed on 11th February 2015 and were updated, 24th May 2016, 4th April 2018, and, 20th May 2019 to ensure recommendations remain current to the best available evidence; search terms and strategies are detailed in Appendix L.

N.B. A systematic literature search was conducted for the previous iteration of the guideline, therefore, the strategy for this update was to search for studies published from January 2007 onwards. All studies included in the previous guideline were assessed against the eligibility criteria in this current update.

Identifying and appraising evidence of effectiveness

The technical team identified potentially relevant studies for the review question from the search results by reviewing the titles. Studies published in languages other than English were excluded. Two members of the GDG then reviewed the abstracts of these studies using the inclusion/exclusion criteria in the systematic review protocol(s). Full papers were then obtained for those agreed as potentially relevant.

The full papers were then reviewed against the inclusion/exclusion criteria in the systematic review protocol(s) to identify studies that addressed the review question.

The systematic reviews were critically appraised using the AMSTAR tool (See Appendix J) and the studies were critically appraised using the appropriate study design checklists as specified in Developing NICE guidelines: the manual. [286]

Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in Appendix A. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix I**: Critical appraisal of included systematic reviews - AMSTAR 2**

	Arora, C. J. (2020).	**Bae, J. M. (2016).**	**Bae, J. M. (2017).**	**Chang, H. C., (2020).**	**Chen, Y.-J. (2016).**	**Chiu, Y-J. (2018).**	**Jin, J. (2016).**	**Kim, H. J. (2018).**	**King, Y.-A. (2018).**
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Partially Yes	No	Partially Yes	Partially Yes	No	No	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No	Yes	No	No	No	No – a mixture of study designs included.	Yes	No – a mixture of study designs included.	No
Did the review authors use a comprehensive	Yes	Yes	Yes – MEDLINE, EMBASE, Cochrane, and	Partially Yes	Yes – Cochrane, EBM reviews, MEDLINE,	Yes – PubMed, EMBASE, and the Cochrane library	Partially Yes– PubMed, Embase, EBSCO, ISI web	Yes –EMBASE, MEDLINE, Scopus,	Partially Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
literature search strategy?			reference lists were scanned.		CNKI, CEPS, Chinese Biomedical Literature database, WANGFAN. All reference lists were also scanned.	databases. All identified articles were screened for cross references.	of knowledge and reference lists were scanned.	Cochrane, and clinical trials.	
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Unclear – two authors independently extracted the data, but not mentioned if two independent authors performed study selection.	Yes	Yes	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Partially Yes – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of	Yes	No	Partially Yes – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given	No	Partially Y – the authors gave reasons for exclusion of studies after full-text review, but they did not provide references for these studies.	No	No	Partially Yes – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
	studies excluded			a list of studies excluded					studies excluded
Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Partially Yes	Yes	Yes	No	Yes	Partially Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes – the authors provided a RoB summary.	No	Yes	Yes – the authors provided a RoB summary.	Yes – the authors provided a RoB summary.	No	Yes – the authors provided a RoB summary.	Yes
Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	Yes – the included studies did not report source of funding.	No	No	No	No
If meta-analysis was performed did the review authors use appropriate methods for	Yes	Yes – the meta-analysis was performed using the	Yes – authors conducted a single-arm proportional meta-analysis.	Yes	N – the authors combined studies which used five	Yes	Partially Yes – the authors compared various combinations.	Yes – the review authors review authors used	Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
statistical combination of results?		generic inverse variance method.			different oral CHM formulas with great variation in terms of ingredients.			the Mantel-Haenszel method with random-effects weighting.	
For non-randomized studies of intervention, did the authors do the following: (1) Justify combining data in a meta-analysis (2) Use an appropriate weighted technique to combine study results, adjusting for heterogeneity if present (3) Statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available	NA – no meta-analysis conducted of NRSI	NA – only RCTs.	No	No	NA – Only RCTs.	No – no explanation given for combining study designs.	NA – only RCTs.	NA – only RCTs.	No

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
(4) Report separate summary estimates for RCTs and NRSI separately when both were included in the review									
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	No	No	No	Yes	No	Yes	No
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Partially Yes – the authors do report on the RoB, but the impact on the results are not discussed in detail.	No	Yes	Yes	Yes	No	Partially Yes- the authors do report on the RoB, but the results are not discussed in detail.	Yes
Did the review authors provide a satisfactory explanation for, and discussion of,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

	Arora, C. J. (2020).	Bae, J. M. (2016).	Bae, J. M. (2017).	Chang, H. C., (2020).	Chen, Y.-J. (2016).	Chiu, Y-J. (2018).	Jin, J. (2016).	Kim, H. J. (2018).	King, Y.-A. (2018).
any heterogeneity observed in the results of the review?									
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Yes	No	Yes	Yes	Yes	Yes	NA – publication bias was not assessed due to the small number of studies.	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes - no conflicts of interest to declare	Yes – none declared.	Yes – grant from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science.	Yes – the authors received no financial support	Yes – no conflict of interest declared.	Yes – none declared; the authors had no funding source providing the financial support for the conduct of the research.	Yes – none declared	Yes – none declared	Yes – no conflicts of interest to declare

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?	Partially Yes – protocol not registered	No	No	Partially Yes	No	No	Partially Yes	Yes	Partially Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	No	No	No – a mixture of study designs included.	No	Yes – inferred	Yes	Yes	Yes	No

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the review authors use a comprehensive literature search strategy?	Yes	Partially Yes – PubMed, EMBASE, Cochrane, Web of Science, and reference lists were scanned.	Yes – MEDLINE, EMBASE, Cochrane, clinical trials and reference lists were scanned.	Partially Y – the authors searched MEDLINE, EMBASE, Cochrane, DARE, and HTAs. The authors also searched for retractions of studies included in the review. The authors did not provide search terms used.	Yes	Partially Yes – PubMed, Embase, CBMdisc, CNKI, WANFANG and CQVIP. The authors also performed a manual search of reference lists.	Yes –EBM reviews, allied and complementary medicine, CINAHL, EMBASE, MEDLINE, Ovid HealthStar.	Yes	Partially Yes – the PubMed and Cochrane library were independently searched. Reference lists of prior reviews, systematic reviews and trials were also checked.
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	No	Yes	Yes	Partially Y– the assessment process was completed by one author, in consultation with another author.	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the review authors provide a list of excluded studies and justify the exclusions?	Partially Y – have given reasons for exclusion and corresponding numbers excluded in PRISMA diagram, but have not given a list of studies excluded	No	No	No	Yes	No – the authors state the number of excluded studies, but they do not provide a list.	No	Yes	No
Did the review authors describe the included studies in adequate detail?	Yes	Partially Yes	Partially Yes	Partially Yes	Partially Yes	Partially Yes	Yes	Yes	Partially Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Yes - the authors provided a RoB summary	Yes – the authors provided a RoB summary	Yes – the authors performed GRADE	Yes	Yes – the authors provided a RoB summary.	Yes – the Jadad scale was used, the authors provided a summary of the results.	Yes	Yes – the authors assessed the RoB.
Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No	No	No	No	No

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes – fixed effects model used due to no significant heterogeneity.	NA – no meta-analysis	No	Yes	Yes	NA – the authors stated that it was not possible to pool the data from the studies due to the wide differences in outcome measures.	Yes	No – the review authors used random-effects model, but it may have been more appropriate to use fixed-effect due to the small number of studies.
For non-randomized studies of intervention, did the authors do the following: (1) Justify combining data in a meta-analysis (2) Use an appropriate weighted technique to combine study results, adjusting for heterogeneity if present (3) Statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw	No	NA – only RCTs.	NA – no meta-analysis.	NA – no meta-analysis.	No	NA – only RCTs.	NA – no meta-analysis.	NA – Only RCTs.	NA – only RCTs.

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
data when adjusted effect estimates were not available (4) Report separate summary estimates for RCTs and NRSI separately when both were included in the review									
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	Yes	NA- no meta-analysis.	NA – no meta-analysis.	No	Partially Yes	NA – no meta-analysis.	Yes	No
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	Partially Y- the authors do report on the RoB, but the results are not discussed in detail.	Partially Y- the authors do report on the RoB, but the results are not discussed in detail.	No	Yes	Yes	Yes	Yes	No

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	NA – publication bias was not assessed due to the small number of studies.	NA – no quantitative synthesis was conducted.	NA – no quantitative synthesis was conducted.	Yes	Yes	No	Yes	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes – no conflicts of interest to declare	Yes – the project was funded by the National Natural Science Foundation of China.	Yes – none declared	Yes – none declared.	No	Yes – none declared.	Yes – none declared; during the duration of this project Szczurko received a Complementary and Alternative Medicine in Paediatrics Masters Scholarship from the Sick Kids Foundation; Boon was funded as a Canadian	Yes	Yes – none declared. The work was supported (not stated how) by the Vitiligo Research foundation; public welfare programme, ministry of health, China.

	Lee, J. H, (2019).	Li, R. (2017).	Lommerts, J. E. (2018).	Matin, R. (2011).	Sakhiya, J. J. (2019).	Sun, Y. (2015).	Szczurko, O. (2008).	Whitton, M. E. (2015).	Xiao, B.-H. (2015).
							Institutes of Health Research New Investigator.		

Abbreviations: CHM, Chinese herbal medicine; NA, not applicable; N, no; RCT, randomized controlled trial; RoB, risk of bias; Y, yes

Appendix J.The GDG was consulted about any uncertainty regarding inclusion or exclusion.

Type of studies

See relevant systematic review protocols (See Appendix A)

Type of analysis

Relevant data were extracted from the studies using the Review Manager (RevMan) 5.3 software package. Where relevant data were incomplete, e.g. standard deviation not provided for the mean change (from baseline) in continuous outcome values, the corresponding authors were contacted. Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate the risk ratios (relative risk). The absolute risk difference was also calculated using GRADEprofiler 3.6 software package, using the event rate in the control arm of the results.

When possible, meta-analyses were conducted to combine the data given in all studies for each of the outcomes of interest for the review question (see Appendix A).

Where relevant, the GDG specified that certain data should be stratified, meaning that studies that varied on a particular factor were not combined and analysed together. Where stratification was used, this is documented in the individual systematic review protocols (see Appendix A).

Appraising the certainty of the evidence by outcomes

The evidence for outcomes from the included randomized controlled trials (RCTs) was evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (www.gradeworkinggroup.org/). The software was used to assess the quality of each outcome, considering individual study quality and the meta-analysed results.

Each outcome was first examined for each of the quality elements listed and defined in Table L.1.

Table L.1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias *(i.e.study limitations)*	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional and assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. The 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example, a result may be consistent with both clinical benefit AND clinical harm) and thus, be imprecise.
Publication bias	Publication bias is a systematic under/overestimation of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an over-estimate of the effectiveness of that outcome.
Other issues	Sometimes, randomization may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be considered. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the four main quality elements (risk of bias, indirectness, inconsistency and imprecision) used to assess overall certainty of evidence were appraised for each outcome are given below. Publication or other biases were only taken into consideration in the quality assessment if it was apparent.

(a) Risk of bias

The key domains of bias for RCTs are listed in Table L.2. Each outcome had its risk of bias assessed within each paper first. For each outcome, if there were no issues with any of the domains, the risk of bias was given a rating of "0". If there were issues with just one domain, the risk of bias was given a "serious" rating of "-1", but if there was risk of bias in two or more domains the risk of bias was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by considering the weighting of studies according to study precision.

Table L2: Principal domains of bias in randomized controlled trials

Limitation	Explanation
Selection bias – sequence generation and allocation concealment	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of 1) knowledge of that participant's likely prognostic characteristics and 2) a desire for one group to do better than the other.
Performance and detection bias – lack of patient and healthcare professional blinding	Patients, care-givers, those adjudicating and/or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of group can influence 1) the experience of the placebo effect, 2) performance in outcome measures, 3) the level of care and attention received, and 4) the methods of measurement or analysis, all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from loss of data beyond a certain level which is not accounted for. Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: Stopping early for benefit observed in randomized trials, particularly in the absence of adequate stopping rules Use of unvalidated patient-reported outcomes Lack of washout periods to avoid carry-over effects in crossover trials Recruitment bias in cluster randomized trials

(b) Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (Chi square $p<0.1$ or I^2 inconsistency statistic of >50%), but no plausible explanation could be found, the certainty of the evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of "-1" if the I^2 was 50-74%, and a 'very serious' score of "-2" if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an $I^2 < 50$), the GDG took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation, the certainty of the evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

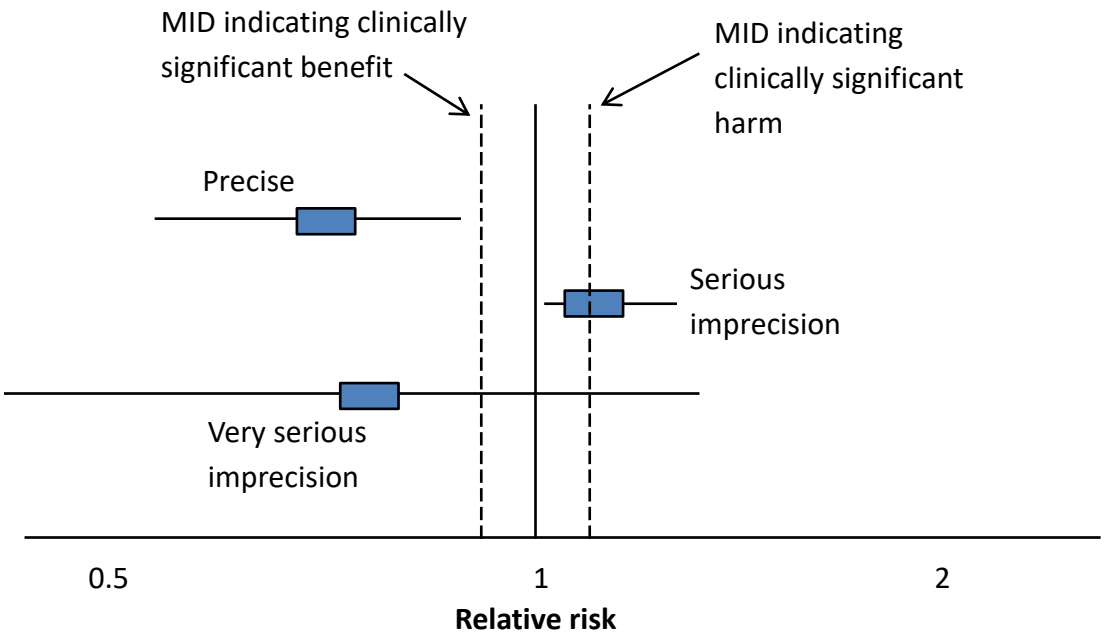
(c) Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for risk of bias, each outcome had its indirectness assessed within each paper first. For each paper, if there were no sources of indirectness, this was given a rating of 0. If there was indirectness in just one source (for example in terms of population), indirectness was given a 'serious' rating of -1, but if there was indirectness in two or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of -1 each for that outcome, the overall score for that outcome would probably tend towards -1.

(d) Imprecision

The criteria applied for imprecision were based on the confidence intervals for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. For categorical/dichotomous outcomes, if either of the 95% confidence intervals of the overall estimate of effect crossed one of the MID lines, imprecision was regarded as serious and a 'serious' score of -1 was given. This was because the overall result, as represented by the span of the confidence intervals, was consistent with two interpretations as defined by the MID (for example, no clinically important effect and either clinical benefit or harm). If both MID lines were crossed by either or both the confidence intervals, then imprecision was regarded as very serious and a 'very serious' score of -2 was given. This was because the overall result was consistent with three interpretations defined by the MID (no clinically important effect and clinical benefit and clinical harm). This is illustrated in Figure L.1.

Figure L.1: Illustration of precise and imprecise outcomes



The position of the MID lines is ideally determined by values as reported in the literature. “Anchor-based” methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or “anchoring” them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, the minimum amount of change in an outcome necessary to make a patient decide that they felt their QoL had “significantly improved” might define the MID for that outcome (e.g. DLQI ≥4 for psoriasis). MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect QoL, or health. For categorical/dichotomous variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, as so are not amenable to patient-centred “anchor” methods.

In the absence of literature values, the alternative approach to deciding on MID levels is the “default” method, as follows:

For categorical/dichotomous outcomes, the MIDs are taken as RRs of 0.75 and 1.25. For ‘positive’ outcomes such as ‘patient satisfaction’, the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line

denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm. No appropriate MIDs for the outcomes were found in the literature and the GDG agreed that the default MID was appropriate.

Non-comparative studies

When higher quality studies with a comparator arm are lacking, data and information from case series and case reports are presented as 'tabulated narrative findings' (Appendix H**: Narrative findings from non-comparative studies**). The assessment of these studies is more subjective and therefore consensus opinion amongst clinical experts on the GDG played a more important role.

Grading the certainty of clinical evidence

Once an outcome had been appraised for the main certainty elements, an overall certainty grade was calculated for that outcome. The scores from each of the main certainty elements (0, -1 or -2) were summed to give a score that could be anything from 0 (the best possible) to -3 (the worst possible, as scores were capped at -3). This final score was then added to the starting grade that had originally been applied to the outcome by default, based on study design.

For example, all RCTs start as 'HIGH' (0 points) and the overall certainty became 'MODERATE', 'LOW' or 'VERY LOW' if the overall score was -1, -2 or -3 points, respectively. The significance of these overall ratings is explained in Table L.3. The reasons used for downgrading were specified in the footnotes of the GRADE tables. On the other hand, observational interventional studies started at 'LOW', and so a score of -1 would be enough to take the grade to the lowest level of 'VERY LOW'. Observational studies could, however, be upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect, as long as they had not been downgraded already due to risk of bias.

Table L.3: Overall certainty of outcome evidence in GRADE

Level	**Description**
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low	Any estimate of effect is very uncertain

For each comparison, e.g. drug A vs. placebo, the certainty of the body of evidence is determined by the majority of the lowest certainty ratings amongst the ***critical*** outcomes; these are featured in the LETR table (Appendix C).

Practical and economic considerations

Where relevant, cross-references were made to NICE guidance and associated health economic evaluation. Drug acquisition costs, resource use and practical considerations based on the experience of the GDG were also considered. Formal health economic analyses were not performed.

Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Summaries of the clinical evidence and overall certainty of the evidence (Appendix C**: Linking Evidence To Recommendation (LETR)**

REVIEW TITLE/QUESTION:
(Q1) In people with vitiligo, what is the clinical effectiveness and safety of topical therapies compared with each other, with placebo or combination of topical plus other active therapies?
(Q3) In people with vitiligo, what is the clinical effectiveness and safety of systemic therapies compared with placebo, other active therapies, or combination of systemic plus other active therapies?
(Q4) In people with vitiligo, what is the clinical effectiveness of a course of light therapy (NB-UVB, PUVA, PUVA-sol) compared with each other, other active therapies, placebo or combination of light therapy plus other active therapies?
(Q5) In people with vitiligo, what is the clinical effectiveness of a course of laser or excimer light therapy compared with each other, other active therapies, placebo or combination of laser or excimer light therapy plus other active therapies?
(Q7) In people with vitiligo, what is the clinical effectiveness and safety of one combination therapy compared to another combination?
(Q8) In people with vitiligo, what is the clinical effectiveness and safety of surgical therapies compared with placebo or other treatments?
(Q9) In people with vitiligo, what psychological interventions are available and what is the effectiveness of these psychological interventions compared with other treatments?
(Q10) In people with vitiligo, what is the clinical effectiveness of skin camouflage compared with placebo, other interventions or combination of skin camouflage plus other active therapies?

(Q11) In people with vitiligo, what is the clinical effectiveness complementary therapies compared with placebo, other interventions or combination of complementary therapies plus other active therapies?	
Relative values of different outcomes	The GDG considered the following outcomes for Q1, Q3, Q4, Q5, Q7, Q8, Q9, Q10, Q11: **Critical** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Re-pigmentation ≥75% (9) • Patient rating of appearance of vitiligo (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) **Important** • Re-pigmentation ≥50% (6) • Cessation of spreading of vitiligo (6) • Maintenance of gained re-pigmentation (6) • Tolerability/ burden of treatment (5)
	Ranked outcomes according to our guideline development protocol1 which uses the GRADE methodology (9-7 Critical for decision making; 6-4 Important but not critical for decision making; 3-1 not important for decision making), as agreed between clinicians and patients.
REVIEW TITLE/QUESTION: **(Q2)** In people with vitiligo, what is the clinical effectiveness and safety of depigmentation treatment compared with other active treatments or placebo?	

Relative values of different outcomes	The GDG considered the following outcomes for Q2: **Critical** • Change in psychological well-being (e.g. signs of depression or anxiety) (9) • Degree of depigmentation (9) • Patient rating of appearance (patient global assessment/colour matching/cosmetic acceptability) (9) • Harms of treatment (8) • QoL (7) **Important** • Risk of re-pigmentation (6) • Tolerability/burden of treatment (5)
REVIEW TITLE/QUESTION: **(Q6)** In people with vitiligo, who have received large doses of PUVA (more than 150 treatment sessions) or NB-UVB (more than 150 treatment sessions), what is the risk of developing premalignant or malignant skin changes compared with people who have not received light therapies and which individuals are at a particular risk?	
Relative values of different outcomes	The GDG considered the following outcomes for Q6: **Critical** • Melanoma • SCC **Important** • Basal cell carcinoma • Other skin cancers • Intraepidermal carcinoma (Bowen's disease/SCC *in situ*)

	Less important • Actinic keratoses
The wording for recommendations is standardized so that they are clearly identifiable, unambiguous and specific: "Offer1" or "Do not offer" (strong recommendation ↑↑ or ↓↓) [an intervention] to patients with [skin disease] + [any relevant conditions] - [1or] similar, e.g. "Use", "Provide", "Take", "Investigate", etc.) "Consider" (weak recommendation ↑) [an intervention] for patients with [skin disease] + [any relevant conditions] The GDG is aware of the lack of high-quality evidence for some of these recommendations, therefore strong recommendations with an asterisk (*) are based on available evidence, as well as consensus and specialist experience.	
Balance between desirable and undesirable effects	**<u>Summary of included systematic reviews</u>** A total of eighteen systematic reviews were identified and found eligible for inclusion.[2-19] (see Appendix E) The main findings include: • A combination of various treatments with light or laser therapy is an effective treatment for vitiligo2 [12,14-19.] • In particular, a combination of topical calcineurin inhibitors with excimer laser/light is more effective than laser/light/calcineurin inhibitor monotherapy4,15,16,19, but its use is cautioned due to the risk of skin cancers.[10] • Excimer laser (308 nm) showed equivalent efficacies to 308 nm excimer lamp and NB-UVB concerning repigmentation rate.[5] • There is a lack of high-quality studies investigating micropigmentation, depigmentation, and cosmetic camouflage.[2] • Natural health products such as Gingko biloba could provide beneficial results in combination with light therapies2 or as monotherapy8, but further investigations are necessary. • Chinese herbal medicines have shown some effectiveness when combined with NB-UVB, but the evidence is limited due to the short follow-up period and low quality of the trials.[7] • The use of fractional CO2 in combination with conventional treatments may be considered as a safe adjunct therapeutic option for adult patients with refractive non-segmental vitiligo.[9,12,18] however, heterogeneity was high amongst the included studies. Future research is needed to investigate the interaction between ablative therapy and conventional treatments for vitiligo.

- Topical calcineurin inhibitor monotherapy is effective on the face and neck, especially in children, therefore is a potential treatment option in children where phototherapy is not suitable [16]

One systematic review publication covering the effectiveness and safety of corticosteroids (oral and topical), oral levamisole, topical immunomodulators, topical vitamin D analogues, PUVA (oral and topical) and NB-UVB formulated treatment recommendations for adults and children.[3]

Summary of included comparative studies

A total of 57 comparative studies20-76 (44 RCTs involving 2809 participants and 14 cohort studies involving 1503 participants) were included (see Appendix E). The sample size of the studies was of a small to large range (15-470 participants) and the range of follow-up was short (1-12 months).

Of the 57 comparative studies, 49 studies reported outcomes with extractable data that was inputted into RevMan.[20-32,34-40,45-50,53-74,76] The remaining eight studies were summarised and not included in quantitative analysis (see Appendix F).[33,41-44,51,52,75]

It was only possible to pool the results of two studies [59,60,] this was due to the heterogeneity of interventions, outcomes, and follow-up time amongst the studies; only single-study forest plots were produced for the remaining included studied. Additionally, many of the forest plots showed imprecision due to the small sample sizes and large confidence intervals; this resulted in a downgrading of the quality of evidence (see GRADE tables – **Error! Not a valid bookmark self-reference.**)
Twentyone of the 49 studies showed outcomes with statistically significant results ($p<0.05$; test for overall effect) when inputted into RevMan.[20,23,27,30,38,47,49,53,54,57,59,60,62,65,67-69,72,73,76]

Summary of included within-patient studies

A total of 54 comparative within-patient studies77-116 [102,117-128] (33 RCTs involving 1,260participants and 21 non-randomized cohort studies involving 648 participants) were identified investigating topical, combination, complementary, light, and surgical therapies (See Appendix G**: Narrative findings from within-patient studies**). The sample size of the studies was of a very small to moderate range (9-135 participants) and the range of follow-up was short to moderate (2 weeks – 15 months).

It was not possible to extract data from within-patient studies into RevMan to produce forest plots as the unit of randomization is one half of each participant. The number of patients involved, i.e. the denominator, would have been

doubled and any pooled estimate of effects underestimated. However, it was possible to calculate the risk ratio and standard error for two outcomes (repigmentation ≥ 75% and repigmentation ≥ 50%) from two within-patient studies.[81,97]

Summary of included non-comparative studies

As some review questions lacked higher quality evidence (RCTs and cohort studies), lower quality non-comparative studies were included (except for laser and light monotherapy where there are sufficient comparative studies).

A total of 41 non-comparative studies12,129-165 [166] (25 prospective case series involving 2,750 participants; 14 retrospective case series involving 1864 participants; one case study involving two participants; one case report) were identified investigating topical, depigmentation, systemic, combination, surgical, complementary, skin camouflage therapies (see **Error! Reference source not found.**). The sample size of the studies was of a very small to high range (1 – 854 participants) and the range of follow-up was short to long (6 weeks – 6 years).

Topical therapies

There is a lack of high-certainty evidence for the use of topical therapies for vitiligo.

In total, six systematic reviews investigating topical therapies were identified.[2-4,12] All four systematic reviews showed topical therapies in combination with other therapies, particularly light or laser, to be better ($p<0.05$) at achieving repigmentation compared with topical monotherapies (see Appendix E).[2-4,12,15,16]

The Cochrane review2 reported that side effects including folliculitis, acneiform lesions, hypertrichosis, itching, redness, telangiectasia, skin thinning, and atrophy were more common with the use of topical corticosteroids. Combination therapies such as a topical intervention with light therapy seemed to increase repigmentation.

One systematic review3 included children with vitiligo and reported improvement in achieving ≥75% repigmentation at 6 months with clobetasol propionate compared with placebo ($p<0.05$). Despite a lack of evidence about the benefits of different strengths of corticosteroids to use topically, the consensus from the review was that potent or very potent topical corticosteroids should be considered first-line therapy in adults or children, except in long-standing lesions; long-term therapy could lead to side effects of atrophy, striae, and telangiectasia. Based on observational studies in adults, the authors

	suggested that topical immunomodulators may be equally efficacious to topical corticosteroids; there was there was insufficient evidence to recommend calcipotriol in adults, children or young people. Another systematic review included eight RCTs4. A total of three analyses showed that topical calcineurin inhibitors, vitamin D3 analogues, or corticosteroids in combination with excimer laser/light therapy were better at achieving ≥ 75% repigmentation compared with excimer laser/light therapy alone ($p<0.05$). Furthermore, another systematic review12 showed that CO2 laser in combination with conventional therapies (topicals/UVB/sun exposure/surgery) was better ($p = 0.03$) at achieving > 50% repigmentation compared with conventional therapies alone. Two systematic reviews [15,16] investigated the use of calcineurin inhibitors in combination therapy compared with calcineurin inhibitor monotherapy. Calcineurin inhibitors were shown to be effective as a monotherpapy on the face and neck in children16 There was some evidence to suggest that topical calcineurin inhibitors in comination with phototherapy have a synergistic effect, but it is difficult to draw solid conclusions due to the heterogeneity and high risk of bias associate with the studies included in the systematic reviews. A total of 28 additional comparative studies20-23,41,46-48,54-56,59,60,64,70,77-88,100 of these studies, 14 were within-patient studies77-88,100,110 and four non-comparative studies129,130,143,144 were identified from the search. The results from the comparative studies, in general, showed that combination treatments including topical therapies were more successful at achieving repigmentation compared with topical monotherapies ($p<0.05$) in six studies20,23,54,59,60,77 (see Appendix E). There has been new interest regarding the use of Janus Kinase inhibitors for vitiligo. Two of the non-comparative studies investigated the use of ruxolitinib 1.5% cream.[129,130] Both studies revealed that patients experienced some repigmentation, with improvement for facial vitiligo ($p<0.05$). But these studies had a small sample size of eight and twelve patients (see Appendix H**: Narrative findings from non-comparative studies**). Based on the evidence, topical corticosteroids would be a sensible first-line therapy, though limited by their potential side effects. Topical calcineurin inhibitors could be used as an alternative to reduce side effects, especially in areas where these are more likely to occur, such as the face; but the optimal regimen cannot be defined based on the evidence. Several other agents have been investigated for treatment of vitiligo, but generally the evidence is weak, so preventing the GDG from

	making recommendations for specific topical therapies. However, there is a suggestion that where topical therapies alone fail to increase repigmentation, the addition of light therapy is a sensible next step. **Recommendation ↑↑:** Offer a potent or very potent topical corticosteroid once daily to minimize potential side effects to people with vitiligo as the first-line treatment in primary or secondary care, avoid periocular area. **Recommendation GPP:** Discuss with people with vitiligo the amount of topical corticosteroids to be used, the site of application, and the safe use of a potent or very potent topical steroid when used correctly. **Recommendation ↑:** Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo as an alternative to potent or very potent topical corticosteroids. **Recommendation ↑:** Consider topical tacrolimus 0.1% ointment twice daily under occlusion on photo-exposed areas only in people with non-facial vitiligo as an alternative to potent or very potent topical corticosteroids. **Recommendation GPP:** Consider an intermittent regimen of once daily application of potent or very potent topical corticosteroids with or without topical calcineurin inhibitors (more evidence for tacrolimus), factoring the risks and benefits, in people with vitiligo especially in areas with thinner skin, e.g. periocular region, genital area and skin flexures. Examples of intermittent regimens would include: • 1 week of potent or very potent corticosteroids and at least 1 week off • 1 week of potent or very potent topical corticosteroids alternating with ≥ 1 week of topical calcineurin inhibitor. Topical corticosteroids could be used for longer than 1 week in the intermittent regimen, after consideration of the risks and benefits. **Recommendation GPP:** Reassess the use of topical treatments (R10-R14) every 3-6 months in people with vitiligo to check for improvement. The use of periodic medical photographs may help assess these changes. **Θ** There is insufficient evidence to recommend topical vitamin D analogues in people with vitiligo.

Future Research Recommendation: Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of topical JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.

DEPIGMENTATION

The evidence for depigmentation therapies is very limited, the identified systematic reviews did not include studies investigating depigmentation therapies, and the GDG identified only one comparative study. [61] There were five non-comparative studies identified,[131-135 four] of which investigated the use of lasers131-133,135 (See Appendix H**: Narrative findings from non-comparative studiesError! Reference source not found.**).

The difference between facial and extra-facial depigmentation was assessed in one comparative study (n= 40).[61] Extra-facial depigmentation [Phenol peel 88%/Cryotherapy/Q-switched (QS) Nd:YAG laser] was shown to be more effectiveve at achieving > 90% depigmentation than facial depigmentation using trichloroacetic acid (TCA) in combination with Qs Nd:YAG (TCA peel 25%/TCA peel 50%/Qs Nd:YAG laser) (p=0.05) and higher overall patient satisfaction.[61]

Data from the four studies131-133,135 identified that the use of lasers ranged from QS ruby laser, QS Nd:YAG laser or a 20 to 755 nm laser. The mean duration of follow-up ranged from 13 to 36 months. The median number of sessions to achieve a complete depigmentation ranged from one to six sessions.[131-133,135]
One study (n=53) showed, monobenzyl ether of hydroquinone to be effective at depigmenting the skin, but the repigmentation was high (78%) after the end of treatment in patients who had achieved successful depigmentation. Patients were followed-up from onset of treatment for an average of 5.4 years; the two commonest side effects included a noxious sensation and an irritant dermatitis.[134]

One study (n=22) assessed cryotherapy and/or 755nm laser therapy; depigmentation varied according to body site with better results on the trunk and worse on the peripheries (p=0.013).[135] A study (n=15) investigating the use of QS Nd: YAG laser at 532-nm wavelength found > 90% resolution of pigmentation in 13 of 15 patients, these patients did not experience relapse at 3-month follow-up.[133] Laser assisted depigmentation with QS laser achieved complete depigmentation in all patients, however the sample size was small (n=6) and included females only. One third of the patients had no relapse, complete repigmentation was observed after 21 months in one patient. Side-effects were limited to transient purpura and crusts. In another small study (n=7), 48% of the 27 included patients treated with QS laser showed ≥75% depigmentation, and the results were better in patients with active disease than those with stable disease (p=0.046).[132]

Recommendation GPP: Consider depigmentation therapies in people with extensive vitiligo on visible sites, in whom the condition is having a negative psychological impact. This should be done after adequate psychological assessment and/or intervention. Please refer to the supplementary information document for further details.

Systemic therapy

There is a notable lack of evidence for the use of systemic therapies for vitiligo. Only a very small number of poor-quality studies reporting a variety of outcome measures, and mainly using systemic therapies in combination with other modalities were identified.[24,25,147,148,167]

The Cochrane systematic review identified 13 studies examining systemic therapies for the treatment of vitiligo.[2] Analysis of three RCTs were reported for treatments and outcomes relevant to this guideline. One RCT (n= 86) showed that weekly oral minipulse therapy (OMP) of betamethasone 0.1 mg/kg of body weight on two consecutive days for 3 months then tapering of the dose by 1 mg/month over 3 months, in combination with NB-UVB, was better at achieving ≥75% repigmentation than OMP alone [RR= 7.41 (95% CI, 1.03 – 53.26), p=0.014].[168] This was not the case for OMP in combination with PUVA or BB-UVB versus OMP alone. Adverse events included weight gain in 37%-50% of patients in both groups.

The second RCT (n=60) showed that azathioprine plus PUVA to be better at achieving≥75% repigmentation than azathioprine alone (9 patients in combination group versus 0 in PUVA alone) [RR=17.77 (95% CI, 1.08 – 291.82), p=0.002].[169] Adverse events included gastric upset in two patients on azathioprine. No cases of malignancy were seen up to 2 years follow-up.

The third RCT did not report on repigmentation.[170] The study assessed the effect on QoL, which found no statistically significant difference in DLQI improvement with the addition of oral levamisole to topical mometasone furoate compared with oral placebo plus topical mometasone furoate.

We identified two further RCTs, not included in the Cochrane review from our search.[24,25] One study (n=50) of minocycline 100 mg daily compared with dexamethasone OMP 2.5 mg on 2 consecutive days a week showed minocycline to be slightly better but this was not statistically significant [RR=3.00 (95% CI, 0.33 – 26.92), p=0.33].[24] Adverse events were common in both groups (20-28%) including hyperpigmentation in the minocycline group and weight gain in the steroid group. In the second study (n=52) there was a similar reduction in the vitiligo diseases activity score for methotrexate and dexamethasone

	OMP; the authors concluded that both drugs demonstrated equal efficacy.[25] Adverse events were common in both; some patients treated with methotrexate experienced nausea and some of those treated with dexamethasone experienced weight gain and acne. Recent reports have suggested that the new JAK inhibitor, tofacitinib, may be effective for vitiligo. Three studies of very low-quality investigating tofacitinib were identified, including a total of 13 patients.[147,148,167] The largest series of 10 patients147 showed a small mean decrease in body surface area (BSA) affected with vitiligo, particularly in areas exposed to the sun or NB-UVB. A further report of two patients treated with oral tofacitinib in combination with NB-UVB showed ≥75% repigmentation,[12] and a case report of tofacitinib monotherapy showed partial repigmentation. No adverse events were identified other than respiratory tract infection in two patients. In summary, there is currently very poor evidence for systemic treatment in vitiligo. OMP steroid in combination with NB-UVB may have an additional benefit compared with NB-UVB alone but must be balanced against a significant risk of side effects. Azathioprine in combination with PUVA may be beneficial171 but the Summary of Product Characteristics (SmPC) for azathioprine states that 'An increased risk of skin tumours have occurred in patients during treatment with azathioprine' and that 'Patients should be warned about undue exposure to the sun or UV rays.' The GDG feels that the risk of potential malignancy is too high to recommend this combination. The studies above did not include children or did not analyse children separately. Safety concerns of systemic treatment, including OMP steroids are greater in children than adults. **Recommendation ↑:** Consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg/month for a further 3 months in combination with NB-UVB in people with rapidly progressive vitiligo to arrest activity of the disease after careful consideration of risks and benefits (see R18). **Recommendation↓↓:** Do not offer azathioprine in combination with PUVA (and NB-UVB) to people with vitiligo due to the risk of malignancy.

Recommendation GPP: Consider an equivalent dose of alternative oral corticosteroids in people with rapidly progressive vitiligo if betamethasone is not available.

Θ There is insufficient evidence to recommend any currently available systemic treatments as monotherapy for people with stable vitiligo. However, there is some evidence for their use in combination with other treatments for rapidly progressive vitiligo (see R17 and R18).

Θ There is insufficient evidence to recommend minocycline, methotrexate or tofacitinib for people with vitiligo.

Future Research Recommendation: Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of oral JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.

Light and laser therapy

NB-UVB

NB-UVB was introduced for the treatment of non-segmental vitiligo (NSV) in 1997 when it was shown to be as efficient as topical PUVA with fewer side effects.[33] Since then, it has replaced PUVA as the preferred phototherapy choice. NB-UVB is at least as effective as PUVA in treating vitiligo.[172] The match of repigmentation to healthy skin colour is better with NB-UVB than with PUVA.[173] Moreover, NB-UVB has been shown to be more effective at achieving >50% repigmentation and at inducing repigmentation in unstable vitiligo compared with PUVA.[26]

A meta-analysis showed that there was no statistically significant difference between NB-UVB and 308 nm excimer laser in achieving ≥ 75% or 100% repigmentation (p>0.05). More patients achieved ≥ 50% repigmentation with 308nm laser than with NB-UVB treatment, but the risk ratio was small [two studies, RR=1.39, (95% CI 1.05-1.85); p=0.002].[5]

The Cochrane systematic review included several RCTs which assessed NB-UVB as monotherapy and in combination with other treatments.[2] Generally, the Cochrane review showed NB-UVB in combination with other therapies to be more effective

	than NB-UVB monotherapy at achieving ≥ 75%. The combination of NB-UVB with antioxidant pool (alpha lipoic acid, vitamin C, E and fatty acids) seems to be more effective in achieving ≥75% repigmentation than NB-UVB alone ($p<0.05$).[174] The combination of NB-UVB with topical pimecrolimus was more effective in achieving ≥75% repigmentation of the facial lesions than NB-UVB with placebo ($p<0.05$); there was no statistically significant difference between the two groups on other body areas.[175] The combination of NB-UVB with oral vitamin E was shown to be slightly better but not statistically significant in obtaining >75% repigmentation than NB-UVB alone.[28] A combination of NB-UVB with topical calcineurin inhibitors (meta-analysis; two studies) or topical vitamin D3 was slightly better at achieving ≥75% repigmentation, but this was not statistically significant.[10] A more recent systematic review has shown that topical NB-UVB in combination with topical calcineurin inhibitors [3 studies, RR=1.79, 95% CI (1.06 - 3.01), p=0.03] or 5-FU injection [1 study, RR=7.25, 95% CI (2.71 - 19.36), p<0.0001] or ER: YAG laser ablation and topical 5-FU in combination with NB-UVB [1 study, RR=5.60, 95% CI (2.31 - 13.59), p=0.0001] or CO_2 laser [2 studies, RR=7.00 (1.30 - 37.60), p=0.02] is superior to NB-UVB monotherapy at achieving ≥75% repigmentation.[19] An additional systematic review conducted in 2020 has also shown that tacrolimus in combination with NB-UVB is slightly better at achieving ≥75% repigmentation [2 studies, RR 1.34; 95% CI (1.05 – 1.71), p=0.02].[15] An additional 18 comparative studies26-29,34,62,66,73,91,94,95,103-105,109,110,118,120,122 were identified that were not included in the systematic review or reported outcomes not covered by the included systematic reviews. Ten of the 19 additional studies were within-patient studies.[91,94,95,103-105,109,118,120,122] Six of the ten within-patient studies showed NB-UVB in combination with another therapy provided more effective repigmentation than NB-UVB monotherapy; one study (n=20) recruited children (5-14 years old) and showed NB-UVB in combination with tacrolimus 0.03% ointment compared with NB-UVB monotherapy was slightly better but not statistically significant at achieving >50% or >75% repigmentation.[103] One within-patient study (n=25) showed that NB-UVB in combination with topical calcipotriol did not result in greater repigmentation when compared with NB-UVB therapy alone.[109] Of the remaining six studies,[26-29,34,62] three studies28,34,62 showed combination treatment with NB-UVB compared with NB-UVB monotherapy was slightly better but not statistically significant at achieving ≥50% and ≥75% repigmentation. One study (n=55) evaluated repigmentation using the VASI, combination of afamelanotide implant with NB-UVB was superior to NB-UVB alone ($p<0.05$);[29] however, the degree of repigmentation improved in both treatment groups ($p<0.001$). A further pilot

	study (n=29) showed hand-held NB-UVB home phototherapy compared with placebo was slightly better but not statistically significant at achieving ≥ 75% repigmentation at 4 month-follow-up.[27] The side effects of NB-UVB include erythema, mild burning or pain, pruritus, and dry skin;[6,27,95] these were reported to be well-tolerated by most patients and generally disappeared several hours after treatment. Other side effects included perilesional pigmentation, hyperpigmentation, ecchymosis, and cold sores.[27,176] There is a lack of studies on NB-UVB in children. This is an issue of concern as vitiligo often starts in childhood and early treatment seems to be more effective. However, NB-UVB started early in life is more likely to be associated with a higher cumulative dose and a higher total number of treatments. The maximum number of NB-UVB sessions remains an open question as there is no evidence from the current literature that the skin cancer risk is increased in treated patients.[177-179] The majority of data is from the retrospective studies on psoriasis patients treated with NB-UVB. The GDG has not found any evidence to suggest that there is an increased risk of skin cancer with NB-UVB; there is a need for long-term follow-up studies of vitiligo patients treated with NB-UVB to establish if the incidence of skin cancer may be increased. **Recommendation ↑↑:** Offer NB-UVB (whole body or localised, e.g. home-based hand-held) as first-line phototherapy to people with vitiligo who have an inadequate response to topical therapy and/or with extensive or progressive disease. This may be combined with topical calcineurin inhibitor[†] (more evidence for tacrolimus) or potent topical corticosteroid,[‡] for localised sites. Counsel patients on the significant risk of loss of response upon treatment cessation. [†] **Prior** to combination NB-UVB and topical tacrolimus treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. A shared decision should be made with the person with vitiligo, taking into account other alternatives, the individual's personal and family history of skin cancer risk and the impact of the vitiligo. [‡] **The** evidence for potent topical corticosteroid is limited. Prior to this combination, consider the risk/benefit ratio of the prolonged use of potent topical corticosteroid.

Future Research Recommendation: A prospective, randomized controlled trial evaluating the safety and efficacy of topical tacrolimus combined with NB-UVB compared with commonly used interventions.

Recommendation GPP: Inform people with vitiligo who are eligible for NB-UVB of the requirements (depending on local protocols: a pre-therapy assessment, medical photographs taken prior to and during follow-ups 3-6 months, two to three sessions weekly possible for up to 1 year), and the likely response depending on the affected anatomical site (e.g. the face and trunk usually achieve better repigmentation than acral sites). Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com.

PUVA

In total, four systematic reviews investigated the use of PUVA in treating vitiligo were included.[2,3,6]

A meta-analysis of three studies from the Cochrane review showed an increase in the proportion of patients achieving >75% repigmentation in favour of NB-UVB compared with oral PUVA, but also an increase in the number of patients experiencing adverse effects such as nausea ($p<0.05$), erythema ($p<0.05$) and itching associated with NB-UVB compared with oral PUVA.[2] Moreover, a meta-analysis of two studies reported by another systematic review6 showed NB-UVB compared with PUVA to be slightly better but not statistically significant at achieving >50% or >75% repigmentation. Side effects reported included mild-to-moderate itching, sedation, xerosis, exacerbation of acne lesions, and nausea.

One systematic review3 formulated treatment recommendations for adults and children. The authors came to the consensus that oral PUVA is an effective treatment for vitiligo in adults, and although topical PUVA is associated with fewer adverse effects, it is unlikely to be an effective treatment for vitiligo in adults. The authors did not recommend PUVA for children under the age of 12 due to a risk of cataract formation, and an increased risk of skin cancer.[3]

An additional five comparative studies31,33,41,54,93 were identified from the search.

A single-centre RCT (n=60) investigated PUVA in combination with topical calcipotriol compared with topical calcipotriol monotherapy; combination therapy was better at achieving ≥75% repigmentation at 6-month follow-up ($p=0.008$).[54] Erythema, pruritus, burning, nausea, and vomiting were associated with PUVA in combination with calcipotriol.[54]

	A non-randomized comparative study31 (n=35) showed oral PUVA to be associated with a better improved QoL compared with PUVAsol (p=0.04) and slightly better but not statistically significant at achieving ≥50% and ≥75% repigmentation at 36-week follow-up.[31] A further, non-randomized comparative study investigating a group of patients with vitiligo (n=106) showed 311 nm UVB therapy to be more effective than topical PUVA at achieving repigmentation at 4-month follow-up, however the percentage repigmentation was not reported.[33] Another non-randomized comparative study (n=26) compared calcipotriol monotherapy to calcipotriol in combination with PUVA therapy. But it is difficult to draw conclusions from this study due to various follow-up times, small sample size, and lack of reported data suitable for statistical analysis (see forest plots in Appendix B**: Forest plots**).[41] A within-patient, non-randomized trial (n=23) showed calcipotriol in combination with PUVA to be slightly better but not statistically significant at achieving a marked response (>50% repigmentation) compared with PUVA monotherapy.[93] **Recommendation ↑:** Only consider PUVA/PUVAsol in adults with vitiligo if treatment with NB-UVB is unavailable or has been ineffective. § § For contraindications refer to BAD PUVA guidelines 2016172 The following is guidance from the British Photodermatology Group and the BAD relating to cancer surveillance with the use of UVB and/or PUVA treatment: "There are no limits to the numbers of treatments patients may have. However, the figures of >200 PUVA and >500 UV treatments are thresholds to trigger skin cancer screening review. There will be patients in whom it is clinically appropriate to continue to treat beyond these numbers. Decisions about whether to continue to treat past these arbitrary threshold numbers are the responsibility of the Dermatology Consultant. The Dermatology Consultant must assess the relative risks and benefits of the various treatment options available for each patient. In some patients, the correct decision is to continue beyond these arbitrary threshold figures." (2016, Phototherapy Service Guidance, pg. 35) **<u>Risk of developing premalignant or malignant skin changes in people with vitiligo receiving light therapies</u>** The risk of carcinogenicity in people with vitiligo treated with NB-UVB and PUVA is still unclear. We did not identify any studies investigating the risk of developing premalignant or malignant skin changes in people with vitiligo, who received

large doses of PUVA or NB-UVB compared with people who have not received light therapies. The latter prevent the GDG from making recommendations on this question.

Previous research has shown that the absolute increase in risk of developing SCCs following over 150 PUVA exposures increases from 2.7% (for 100-159 exposures) to 8.8% for over 160 exposures in patient with psoriasis. However, three small studies177,180,181 were unable to detect any definitive increase risk of skin cancer following NB-UVB in psoriasis patients. A larger study of 1380 patients suggested that UVB remains a relatively low-risk treatment for psoriasis.[182]

The GDG would like to make the following suggestions based on the NICE psoriasis guideline183 and the BAD biologics for psoriasis checklist.[184] The aforementioned documents provide indirect evidence based on data from psoriasis population.

Home phototherapy

There was a lack of high-quality studies investigating the use of home phototherapy for the treatment of vitiligo. The included systematic reviews did not investigate home phototherapy, two studies were identified from the search which investigated home-based phototherapy for the treatment of vitiligo.[32]

Hand-held home-based phototherapy compared with institution-based excimer lamp was shown to be slightly better but not statistically significant at achieving ≥50% and ≥75% repigmentation at 6-month follow-up. Similarly, the pilot Hi-Light trial showed hand-held home phototherapy compared with placebo was slightly better but not statistically significant at achieving ≥75% repigmentation at 4-month follow-up.[27] The most recent data from the HI-Light trial has shown hand-held home-based NB-UVB phototherapy in combination with topical corticosteroid (mometasone furoate 0.1%) to be superior to topical corticosteroid monotherapy at achieving ≥75% repigmentation at 9 months [1 study, RR=4.45, 95% CI (1.54 – 12.88), p=0.006]; hand-held home-based NB-UVB monotherapy was shown to be superior to topical corticosteroid monotherapy but this was not statistically significant [RR = 2.30, 95% CI (0.72 – 7.34), p=0.16]. Multiple tools were used to assess the QoL but hand-held home-based NB-UVB was not shown to improve the QoL compared with topical corticosteroid monotherapy. Treatment-related adverse events were less in those using topical corticosteroid therapy. Erythema (grad 3 and 4) in particular was shown to be higher in those receiving topical corticosteroids in combination with hand-held home-based NBUVB compared with topical corticosteroid monotherapy in both adults [RR=12.81, 95% CI (3.10 – 52.89), p=0.0004] and children [RR=7.00, 95% CI (0.90 – 54.32)] and similarly higher in those receiving hand-held home-based NB-UVB monotherapy compared with topical steroid monotherapy in both adults [RR=10.23, 95% CI (2.44 – 42.89), p=0.001] and

children [RR=7.18, 95% CI (0.93 – 55.68), p=0.06].[76] Considering newly emerging evidence that early treatment of vitiliginous lesions seems to be effective,[185-187] home-based targeted phototherapy is a safe option, if done under supervision of a trained clinician.[27,32] Further high-quality RCTs and economic evaluations are needed to assess the clinical and cost effectiveness of home-based phototherapy.

Laser therapies

Targeted laser phototherapies are used for localised vitiligo, especially for small lesions, to avoid side effects due to whole-body irradiation with NB-UVB. Several studies assessed laser and light therapies as monotherapies, and in combination with topical treatments.[2] In particular, combinations of excimer laser with topical calcineurin inhibitors,[188-191] topical corticosteroids192 or topical vitamin D3 analogues193 seem to be more effective in achieving ≥75% repigmentation of vitiliginous lesions than excimer laser alone [RR = 2.57 (95% CI 1.20 – 5.50), p=0.02] and [RR=4.50 (95% CI 1.04 – 19.47), p=0.04] respectively. One RCT (n=233) identified from the search53 showed yiqiqubai granules in combination with 308-nm excimer laser to be more effective in achieving ≥ 50% repigmentation than yiqiqubai granules alone [RR=1.62 (95% CI 1.13-2.34), p=0.010]. A non-validated 5-point scale was used to assess the QoL; combination therapy of 308-nm excimer laser with yiqiqubai granules was better (p<0.05) than 308-nm laser or yiqiqubai granules monotherapy at improving QoL in the following areas: embarrassment, social, and work.[53]

A meta-analysis showed 308 nm excimer laser was slightly better but not statistically significant compared with 308-nm excimer lamp in achieving ≥75% or ≥50% repigmentation (p> 0.05).[5] However, more patients (p=0.002) or lesions (p=0.009) achieved ≥50% repigmentation by 308nm laser than by NB-UVB treatment.[5] Side effects of excimer laser include hyperpigmentation, burning, stinging, moderate-to-severe erythema, oedema, and blisters.[2,5,92]

Several studies reported data for the use of CO2 laser in vitiligo.[9,17,18,23,49,123] One RCT (n = 68 patients) showed that in lesions on hands and feet, a combination of CO2 laser with topical 5-fluorouracil, may be effective for acral, refractory vitiligo in adults unresponsive to other treatments in achieving ≥50% repigmentation [RR=16.80 (95% CI 10.88 – 25.95), p < 0.00001] and ≥75% repigmentation [RR=24.96 (95% CI 14.21 – 43.86), p < 0.00001].[23] In addition, a meta-analysis revealed that using fractional CO2 laser in combination with conventional treatments was more effective at achieving ≥75% repigmentation [RR = 2.80 (95% CI 1.29 – 6.07), p=0.009], and may be considered as a safe adjunct therapeutic option for patients with refractive non-segmental vitiligo.[9] The most common side effects reported were pain, followed by burning sensation, erythema,

	oedema and oozing; other side effects included itching and ecchymosis.[9,49] No infection, scarring or Koebner phenomenon occurred after using fractional CO2 laser.[9] One systematic review [18] showed ablation therapy (CO2 laser in 10 studies and erbium-YAG in 5 stuidies) in combination with other treatments for vitiligo to be superior to treatment without ablation therapy at achieving ≥75% repigmentation [11 studies, OR=5.812, 95% CI (2.194 – 15.3939), p=0.000] and ≥50% repigmentation [11 studies, OR=10.490, 95% CI (4.632 -23.757), p=0.000]. Sub-group analysis showed fractional CO2 laser in combination therapy to be superior to the control at achieving ≥50% repigmentation [6 studies, OR=7.810, 95% CI (1.754 – 34.780), p = 0.007] and marginally superior at achieving ≥75% [5 studies, OR=1.897, 95% CI (0.764 – 4.711), p = 0.168]. Moreover, CO2 laser in combination therapy was superior to control treatment in achieving ≥ 50% repigmentation [7 studies, OR=9.964, 95 % CI (3.107–31.955, p<0.001] and ≥ 75% repigmentation [6 studies, OR=3.901, 95% CI (0.785–19.383), p=0.096]. Non-fractional erbium-YAG laser combination therapy was shown to be superior to the control group in achieving ≥ 50% repigmentation [2 studies, OR = 20.272, 95% CI (1.953 – 210.459), p=0.012] Finally, the GDG found no consensus on the treatment duration or the maximum number of treatments for laser therapies from the studies identified. **Recommendation ↑:** Consider excimer laser or light in people with localised vitiligo in combination with topical calcineurin inhibitors (more evidence for tacrolimus). Prior to treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest. **Recommendation ↑:** Consider CO2 laser in combination with 5-fluorouracil in adults with non-segmental vitiligo on hands and feet if other treatments have been ineffective (apply 5-fluorouracil once daily for 7 days per month for 5 months; CO2 laser treatments once a month for 5 months). This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest. **Θ** There is insufficient evidence to recommend combination treatment of potent or very potent topical steroid with NB-UVB plus CO2 laser for people with vitiligo.

Future Research Recommendation: Prospective, randomized controlled trials evaluating the safety and efficacy of CO2 laser for vitiligo compared with commonly used interventions in adults with vitiligo.

Combination therapies

Generally, combination therapies were shown in systematic reviews to be more effective at achieving repigmentation compared with monotherapies (see Appendix E).[2,4,7,10,14] These comparisons are considered in other sections, according to the monotherapy comparators. This section deals with studies that compared one combination therapy with another combination therapy.

Combination of topical calcineurin inhibitors with ultraviolet and other forms of radiation is generally discouraged194 due to the theoretical increased risk of skin cancer, although there is no firm evidence for this. None of the combination studies in this systematic review assessed long-term outcomes such as incidence of new skin cancers following treatment, so the GDG recommends that the findings regarding the combination of topical calcineurin inhibitors and excimer laser or light be interpreted with caution.

The GDG noted that when comparing one combination treatment with another, the overall quality of studies was poor and there was very little evidence to support one combination over the other.

One RCT (n=50) comparing alpha-lipoic acid with placebo, both combined with betamethasone injections and NB-UVB, showed no statistically significant difference between the two groups in those achieving at least 50% and 75% repigmentation (p>0.05).[36] Nine participants reported nausea or dizziness after taking alpha-lipoic acid, although the time point at which this occurred was not specified (the GDG assumed it was throughout the course of the trial). Seven participants reported weight gain after receiving betamethasone injections, this resolved after cessation of treatment.

One RCT (n=50) compared punch grafting plus PUVA with punch grafting plus topical 0.1% fluocinolone acetonide; PUVA or topical treatment was commenced 4 weeks after punch grafting and treatment was continued for 6 months.[35] Cosmetic acceptability of results at 6 months showed no statistically significant difference between the groups [RR=0.94 (95% CI 0.77 – 1.15), p=0.57]. Adverse events including cobblestoning, infection, and displacement or depigmentation of the grafts occurred in similar rates in both groups.

	A non-randomized study compared (n=32) combination treatment involving monochromatic excimer light with either topical 0.1% tacrolimus, topical 4% khellin, or both.[37] This study was of poor quality with a high risk of bias and small sample size; statistical significance was not reached for any of the outcomes analysed (p>0.05). The GDG identified seven non-comparative studies assessing various other combination treatments for vitiligo (see **Error! Reference source not found.**).[12,149-153,161These] non-comparative studies did not provide robust evidence for any of the combination treatments assessed. The two studies assessing oral methylprednisolone reported gastrointestinal side effects in some participants;[152,153] combination of oral methylprednisolone and topical fluticasone resulted in several cases of cutaneous dermatophyte infections and precipitation of acne.[153] There is some evidence to suggest that the reduction/removal of epidermal H2O2 using NB-UVB (0.15 mJ/cm2)- activated psudocatalase PC-KUS in children is effective at achieving repigmentation in children with vitiligo.[161] The GDG also identified four within-participant studies assessing combination treatments.[89,90,101,102] One within-patient, RCT (n=25) showed a triple combination of fractional CO2 laser plus topical betamethasone and NB-UVB to be better (p=0.042) at achieving at least 50% repigmentation compared with fractional CO2 laser plus NB-UVB only.[89] All participants experienced moderate pain, erythema and oedema due to the laser treatment. A further study (n=26) showed fractional CO2 laser plus topical 0.05% clobetasol propionate and NB-UVB to be slightly better but not statistically significant at achieving >50% repigmentation compared with fractional CO2 laser plus topical 0.05% clobetasol propionate alone. (p=0.065).[90] Participants receiving triple combination treatment experienced more post-treatment pain than the other participants (p<0.001). Korobko *et al*. (2016)[101] compared microneedling combined with latanoprost 0.001% solution or 0.1% tacrolimus ointment; combination therapy was better that 0.1% tacrolimus ointment monotherapy at achieving ≥75% repigmentation (p= 0.0459).[101] Mina *et al.* (2018)[102] compared microneedling combined with 5-flurouracil or 0.1% tacrolimus ointment. The combination of 5-flurouracil with microneedling was better at achieving repigmentation compared with 0.1% tacrolimus in combination with microneedling (p=0.023). Adverse effects such as hyperpigmentation, inflammation and ulceration were observed in patches treated with 5-fluorouracil while in patches treated with tacrolimus, there were no complications observed (p = 0.004).[102]

Although there was some limited evidence to support the use of some combination therapies, the overall quality of the evidence was very low, and no firm recommendations can currently be made for any combination treatment assessed and discussed above.

Surgical therapies

The GDG noted that due to the invasive nature of the surgical procedure it is difficult to design RCT studies that are truly double blinded with placebo control. As a result, many novel techniques are reported as cohort studies of small sample sizes.

In total 7 RCTs were included.[57-59,62,63,71,72] One RCT compared NCES blister roof graft to NCES Thiersch graft, whilst there was no difference in repigementation achieved, greater hyperpigmentation was associated with the NCES Thiersch graft group [RR=8.20; 95% CI (2.56 – 26.30), p=0.0004] [57] and NCES/non-cultured dermal cell suspension (NDCS) was shown to be marginally better than NCES at achieving ≥ 75% compared with NCES [RR=1.89; 95% CI (1.12 – 3.17), p=0.02]. [72] Combining tacrolimus 0.1% with microneedling was shown to be superior to microneedling monotherapy in achieving repigmentation ≥ 75% [RR=2.00; 95% CI (1.14 – 3.52), p=0.02] and repigmentation ≥ 50% [RR=2.09; 95% CI (1.26 – 3.48), p=0.005] at 3-month post-treatment follow-up.[59]

The GDG identified one systematic review which included studies investigating surgical therapies.[2]

The review included a wide range of surgical techniques. Overall melanocyte transplantation resulted in a reduction of DLQI scores in patients ($p<0.05$).[31,195] The main side effects of minipunch grafting techniques showed cobblestoning and variegated appearance of scars.[35] Interestingly this study also found no difference between patients with segmental and non-segmental vitiligo, in their respective response rate. The proportion of patients achieving ≥75% repigmantation was higher in those with blister grafts.[196] Dermabrasion and needling were reported as treatment but without any relevant data to report.

One non-randomized, within-patient study (n=83) compared blister roof grafting (BG), cultured melanocytes transplantation (CMT), and NCES transplantation in the treatment of stable vitiligo.[98] Excellent repigmentation (≥90%) was observed in all treatment methods at 12-month follow-up, with a higher proportion in those receiving BG (76%) compared with CMT (55%) and NCES (53%) (p=0.038, p=0.017, respectively). The study concluded that all methods were effective in treating vitiligo. However, the donor size to treatment area ratio varied according to procedure; BG was used to treat much smaller areas at

	a ratio of 1:1 as opposed to 1:5 for NCES, hence, a like-for-like comparison was not made for the treatment areas, as agreed by the GDG. The treatment was well tolerated; none of the patients developed infection, milia, or visible scarring at any donor or recipient site – this could have been due to the use of CO2 laser for dermabrasion. Another non-randomized, within-patient study (n=10) treated, in total, 39 patches in patients with stable, generalized vitiligo.[99] Nine were treated by melanocytes-keratinocytes transplantation (MKT) alone; ten patches were treated with MKT and excimer laser; another ten treated with excimer laser alone; and ten patches were treated as the control with manual dermabrasion only. At 2-week follow-up, 2/9 patches in the combination group (MKT and laser) showed ≥90% repigmentation, whereas the other groups did not reach this level of pigmentation. The authors conceded that the repigmentation rate is lower for MKT alone than in other reports, they concluded that despite a small sample size there is value of adding MKT to excimer laser ($p < 0.001$). The small sample size and short follow-up period is a limitation of this study; therefore, the results should be interpreted with caution. A multicentre, non-randomized comparative study (n=170) focused on comparing lesion stability with disease stability.[39] Patients with lesion stability (greater than 12 months) and disease stability of only 6 to 11 months were shown to have similar response to various surgical methods [mini-punch grafting (MPG), ultrathin skin grafting (UTSG), and NCES] to patients with overall disease stability of greater than 12 months. This suggests that patients may be able to have surgical treatment earlier if certain lesions are stable, despite their overall disease being progressive. The percentage of patients achieving > 90% repigmentation at 6 months was 45%, 42% and 30% in the NCES, UTSG, and MPG groups, respectively. The number of non-responders (13.3%) was the highest in the MPG group. Adverse effects included perigraft halo and hyperpigmentation. A further five, more recent within-patient studies were identified111-115 investigating microneedling, NCES, NCES in combination with follicular cell suspension (FCS), and melanocyte keratinocyte transplantation (MKTP). But these were of a small sample size and the GDG did not think the evidence was sufficient to make any recommendations. None of the studies listed assessed the change in patients' QoL as a result of treatment; the GDG considered that percentage repigmentation is only one objective measure of successful therapy.

Recommendation ↑: Consider cellular grafting, e.g. blister grafting or cell suspension, in people with stable, segmental or non-segmental vitiligo that is unresponsive to other treatments, and who remain distressed by the condition. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.

Θ There is insufficient evidence to recommend mini-punch grafting in people with vitiligo.

Psychological therapies

There is a dearth of studies that have sought to examine the effectiveness of psychological therapies, interventions, or techniques for the alleviation of distress associated with vitiligo or to facilitate adjustment to the condition.

The Cochrane systematic review2 identified two RCTs examining psychological therapies in patients with vitiligo.[42,43] One of the RCTs (n=16) showed that weekly one-to-one cognitive behavioural therapy (CBT) for 8 weeks was better at improving psychometric measures of body image, QoL, and self-esteem compared with the control group receiving no change in conventional treatment, at 5-month follow-up ($p<0.05$).[42] Twelve participants were eligible to have the progression of their vitiligo assessed through photographs (four were ineligible as they were receiving PUVA treatment, and the others did not consent to be photographed). Independent clinician and researcher ratings indicated changes in five cases, improvement in three CBT cases, and deterioration in two participants in the control group. Clearly, the findings in relation to progression of vitiligo whilst interesting are essentially anecdotal.

Another RCT (n=44) compared eight session group interventions; two parallel groups of CBT and group person centred therapy (PCT) with a control condition within a hospital and community setting.[43] Both active treatments led to significant improvements in comparison to the control group but only on the general health questionnaire, and the interventions were thus judged to be unsuccessful. The other clinical measures which included outcomes such as self-esteem and body image, in addition to disease progression (again measured by review of photographs), did not show improvement. For the CBT groups, improvement in the general health questionnaire were noticeable directly post-treatment and maintained over the duration of the follow-up, whereas for PCT, improvements were only visible at 6-month and 12-month follow-up.

One further RCT44 and one non-comparative prospective case series146 not included in the Cochrane systematic review, were identified from our search.

	The RCT (n=75) compared self-help interventions (administered as pdf leaflets) with a control (no counselling and change in treatment) within a community setting.[44] There were two intervention groups which used CBT techniques to target socially related concerns; one of the interventions was enhanced with a behaviour change technique aimed at facilitating the use of the CBT techniques. A higher percentage of participants showed a reliable change in the enhanced self-help condition compared with the other intervention and control group in the primary outcome measure (a measure of social anxiety) but not in the other outcome variables, which included measures of anxiety, depression, and body image concern. Qualitative feedback on the intervention indicated that participants had found the self-help materials in both active treatment groups useful. There was an overall improvement in mood charts in seven of the eight patients, one patient had worsening of mood scores due to an increase in number of lesions. The non-comparative study (n=13) used five sessions of CBT through five weekly sessions conducted by a dermatology trainee under the guidance of a clinical psychologist.[146] All eight patients who completed the five sessions had a reduction in DLQI, this was meaningfully different in four patients at the end of the five sessions and at 12-week follow-up. Five of the eight patients had meaningful reductions in Skindex-16 scores at the end of the five sessions and at 12-week follow-up. The Cochrane review and our own analysis identified significant limitations with all studies in terms of risk of bias. For example, the Papadopoulos *et al.*[42] study was unable to employ any robust blinding, additionally it only compared an active psychological treatment with receipt of no treatment at all.[42] The Papadopoulos *et al.* (2004)[43] and Shah *et al*. (2014)[44] studies similarly had significant limitations, although they both had active psychological treatment comparison groups as well as control conditions.[43,44] Caution is needed in extrapolating recommendations from these studies given the limitations in both study design and the lack of replication. Despite the limitations within the evidence base, the GDG remains of the opinion that conducting a psychological screening assessment within all levels of care (including within general practice) and providing access to psychological intervention remains an important consideration in the treatment of vitiligo, particularly in secondary care centres where psychological distress may be higher. This opinion is supported by the outcome of the James Lind Alliance Priority Setting Partnership which identified psychological intervention as a priority area.[197] Clinicians should also consider using brief measures of psychological distress in conjunction with vitiligo specific QoL measures such as VitiQoL and VIPs (vitiligo impact patient scale).[198]

	The evidence suggests that people with vitiligo experiencing psychological distress or/and an adverse reaction on their QoL might benefit from psychological interventions delivered within a stepped a care model. Some people might benefit from self-help or guided self-help, whereas other people may require one-to-one therapy or benefit from group intervention. **Recommendation ↑↑:** Offer* information on self-help (e.g. leaflets, books, websites, apps) to people with vitiligo with mild psychological distress. **Recommendation ↑↑:** Offer* referral to psychological services for group or/and individual cognitive behavioural therapy (CBT) to people with vitiligo with moderate-to-severe psychological distress. **Future Research Recommendation:** Prospective randomized controlled trials evaluating the effectiveness of psychological interventions in people with vitiligo. **Skin camouflage** There were no systematic reviews identified which assessed cosmetic camouflage therapies. In total, there were five studies identified which assessed camouflage therapies in patients with vitiligo.[40,45,137,138,199] The only relevant outcome measure from these studies was change in QoL. One RCT (n=144) was identified comparing herbal Iranian skin camouflage preparation with Exuviance cosmetic formulation, both showed an improvement in DLQI ($p<0.05$).[40] The Sabgh formulation was slightly better than the Exuviance cosmetic formulation, but the difference was not statistically significant. There is low quality evidence from one non-randomized comparative study (n=144) showing that one-to-one skin camouflage lessons showed an improvement in DLQI scores compared with patients who did not receive one-to-one skin camouflage lessons ($p<0.05$). These patients were not randomized to treatment and the control group represented a very small subgroup (11 out of 155), who declined treatment and may have had very different baseline characteristics.[45] In a prospective case series (n=62) patients receiving a camouflage sample matching their skin complexion were followed up after at least 1 month and DLQI scores improved after camouflage use ($p<0.05$).[199]

Another prospective case series (n=6) showed that children receiving camouflage therapy workshop along with a family member had a non-significant improvement in cDLQI scores 2 weeks after the workshop. There were only three cases of vitiligo included in the study and these were all female patients with segmental facial vitiligo, representing a specific subgroup of vitiligo patients.[137]

A retrospective case series (n=20) showed that patients using dihydroxyacetone (DHA) for skin camouflage were dissatisfied with the product due to irregular brownish staining and no staining at all.[138]

One study (n=854) online survey was used to estimate the QoL of Chinese vitiligo patients using skin camouflage for > 1 month [median 50 months; range (1 -216)] [166.] The mean (SD) DLQI score was 5.83 (5.75) signifying a small – moderate effect on the patients' QoL. The mean DLQI scores were highest for three domains: daily activities, leisure, and, symptoms and feelings. "Very much" patient satisfaction with camouflage therapy us achieved in 82/854 (9.3%) patients.

The DLQI score was shown to be independent of age, gender, marriage status, occupational status, anogenital involvement, patient perceived severity, symptoms (e.g. itching, pain, sunburn and koebner phenomenon), total cost and degree of satisfaction ($p < 0.05$).

Recommendation ↑: Consider a skin camouflage consultation in people with vitiligo who would like to explore this option.

COMPLEMENTARY therapies

There was very limited evidence identified for complementary therapy use in patients with vitiligo.

The Cochrane systematic review identified one double blind, randomised, placebo controlled small study, which showed Ginkgo Biloba (40 mg orally three times daily) was more effective compared with placebo at achieving ≥75% repigmentation ($p<0.05$).[200] Other complementary therapies identified in this review included pseudocatalase, catalase/dismutase superoxide and tetrahydrocurcuminoid cream, however the results were not reported in a way that would allow analysis of ≥ 75% repigmentation.

A meta-analysis identified showed a superior effectiveness ($p<0.00001$) of Chinese Herbal Medicine (CHM) in combination with NB-UVB compared to NB-UVB alone in achieving ≥50% repigmentation, however this was based on five RCTs, each investigating a different formulation of CHM; the heterogeneity makes drawing any conclusions difficult.[7] Another

	systematic review included trials of poor quality, most studies were poorly reported, often lacking information about dosing frequency, dosage strength, participant withdrawal, statistical analyses, and randomisation.[8] This poor quality makes it difficult to draw any conclusions. Ten further studies were identified from our search.[38,49,50,73,123,139-142,164] Two randomized controlled trials49,50,73 and one non-randomized comparative study38 were identified. Combination treatment of Vitamin E (one capsule of 400 UI orally daily)NB-UVB, and Khellin ointment 4% was shown to be more effective than vitamin E alone at achieving > 50% [RR=14.00 (95% CI 2.08 – 94.24), p=0.007] and > 75% repigmentation [RR=19.00 (95% CI 1.20 – 301.16, p=0.004].[38] Oral compound glycyrrhizin in combination with NB-UVB showed an improvement (p<0.005) in DLQI score compared with oral compound glycyrrhizin alone.[50] Vitilinex lotion/emollient (consisting of herbal bio-actives with anti-oxidant properties) in combination with NB-UVB was shown to be more effective than Vitilinex monotherapy in achieving > 50% repigmentation [RR=1.94 (95% CI 1.27 – 2.97, p =0.002)] and >75% repigmentation [RR=2.59 (95% CI 1.38 – 4.87), p=0.003].[73] Similarly, vitilinex in combination with NB-UVB was shownt to be more effective at achieving >50% and >75% repigmentation, however, this was not a statistically significant result. [73] Six of the eleven studies were non-comparative.[139-142,164,165] One non-comparative study (n=436) investigated climatotherapy involving dead sea bathing and sunshine exposure, this was associated with >50% repigmentation in only 3.9% of 436 patients.[139] A study (n=20) investigating the effect of leech application weekly for 6 months in 20 patients reported >50% repigmentation in 9 of 20 patients and >75% repigmentation in 2 of 20.140 A further non-comparative study (n=42) of Vitalog (containing 80 mg of Stachytarpheta cayensensis Vahl aqueous dried extract) reported 69 of 99 lesions achieving ≥75% repigmentation.[141] Nigella seed oil applied to the hands, face, and genital regions twice daily for 6 month was shown to be effective at achieving ≥ 50% repigmentation, but this was based on a small sample size (47 patches). [164] Autologous non-cultured epidermal cell suspension combined with platelet rich fibrin was also shown to be effective at achiving ≥ 50% repigmentation, but this was also based on a very small sample size (n=7).[165] One non-comparative study (case series) reported on the use of eight different homeopathic compounds over 24 months, 140 of 200 patients achieved 100% repigmentation;[142] 69% of the study population were less than 20 years old, this may be an indicator of the natural history of the disease.

Whilst vitamin E, antioxidant pool, and Ginkgo Biloba were shown to be statistically significantly effective at improving repigmentation, the GDG felt there was insufficient high-quality evidence to make recommendations for these intereventions.

Θ There is insufficient evidence to recommend a specific complementary therapy for people with vitiligo.

Certainty of evidence

TOPICAL THERAPY

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	Betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. betamethasone dipropionate 0.05% cream	Tacrolimus 0.1% ointment vs. placebo	None	CO2 laser + topical 5FU vs. topical 5FU
	Betamethasone dipropionate 0.05% cream + calcipotriene 0.005% ointment vs. calcipotriene 0.005% ointment	†Topical cream (Photocil) + natural sunlight exposure vs. placebo cream + natural sunlight exposure		Topical 5FU vs. CO2 laser
	Betamethasone dipropionate 0.05% cream vs. calcipotriene 0.005% ointment			
	PUVA + calcipotriol vs. calcipotriol			
	Re-pigmenta vs. Bioskin			
	Re-pigmenta + Bioskin vs. Re-pigmenta			
	Re-pigmenta vs. Clobetasol 0.05%			
	Re-pigmenta + Bioskin vs. Bioskin			

	Bioskin vs. clobetasol 0.05% propionate	Tacrolimus 0.1% + microneedling vs. tacrolimus 0.1%		
	Re-pigmenta + Bioskin vs. clobetasol propionate 0.05%	Hand-held NB-UVB + mometasone furoate 0.1% vs. mometasone furoate 0.1%		
	Tacrolimus 0.1% + topical pseudocatalase/superoxide diutase gel vs. tacrolimus 0.1%			
	Tacrolimus 0.03% vs. pimecrolimus 1%			

† Based on important outcomes – no raw data or quality rating for critical outcomes

SYSTEMIC THERAPY

	Certainty of evidence			
Interventio	**Very low**	**Low**	**Moderate**	**High**
	Oral methotrexate (MTX) vs. OMP (betamethasone/dexamethasone)	Minocycline 100mg/day vs. (OMP) 2.5mg dexamethasone	None	None
	Mel + khel + vitamin E vs. Vitamin E			

LASER AND LIGHT THERAPY

	Certainty of evidence			
Interventions	**Very low**	**Low**	**Moderate**	**High**
	home-based hand-held phototherapy vs. institution-based excimer lamp	NB-UVB + Vitamin E vs. NB-UVB	CO2 laser vs. Topical 5FU	Topical 5FU + CO2 laser vs. CO2 laser
		Home-based hand-held NB-UVB treatment vs. placebo	Afamelanotide + NB-UVB vs. NB-UVB	
		†NB-UVB vs. PUVA		Yiqiqubai granule + 308nm excimer laser vs. 308 nm excimer laser
	Bioskin vs. tacrolimus 0.1% + Bioskin	Tacrolimus 0.1% + excimer laser vs. excimer laser		

Bioskin vs. pimecrolimus 1% + Bioskin	Home-based hand-held NB-UVB vs. topical mometasone furorate 0.1%		
Microneedling + NB-UVB + topical triamcinolone vs. NB-UVB			Yiqiqubai granule + 308nm excimer laser vs. yiqiubai granule
Apremilast + NB-UVB vs. placebo + NB-UVB		Halometasone + excimer laser vs. excimer laser	PRP + excimer laser vs. excimer laser
Pimecrolimus 1% + excimer laser vs. excimer laser		Home-based NB-UVB vs. hospital-based NB-UVB	
Home-based NB-UVB vs. outpatient NB-UVB		Vitilinex + NB-UVB vs. NB-UVB	
Home-based hand-held NB-UVB + TCS vs. hand-held NB-UVB			

† Based on important outcomes – no raw data or quality rating for critical outcomes

COMBINATION THERAPY

	Certainty of evidence			
Intervent	**Very low**	**Low**	**Moderate**	**High**
	MEL + khellin 4% + tacrolimus 0.1% vs. MEL + tacrolimus 0.1%	punch grafting + corticosteroids vs. punch grafting + PUVA	None	None

	alpha lipoic acid + betamethasone injection + NB-UVB (combination) vs. placebo + betamethasone injection + NB-UVB (control)	Excimer laser + tacrolimus 0.1% vs. excimer laser + halometasone		
	MEL + khellin 4% + tacrolimus 0.1% vs. MEL + khellin 4%			
	MEL + khellin 4% + tacrolimus 0.1% vs. MEL			
	MEL + tacrolimus 0.1% vs. MEL + khellin 4%			
	MEL + tacrolimus 0.1% vs. MEL			
	MEL + khellin 4% vs. MEL			
	Tacrolimus 0.1% + excimer laser vs. pimecrolimus 1% + excimer laser			

SURGICAL THERAPY

	Certainty of evidence			
Intervent	**Very low**	**Low**	**Moderate**	**High**
	Ultra-thin skin grafting vs. miniature punch grafting	Microneedling + tacrolimus 0.1% vs. microneedling	NCES Blister roof graft vs. NCES Thiersch graft	Non-cultured epidermal cell suspension/non-

	Ultra-thin skin grafting vs. non-cultured epidermal cell suspension			cultured dermal cell suspension vs. non-cultured cell suspension
	Non-cultured epidermal cell suspension vs. miniature punch grafting			
	Cold trypsinization preparation non-cultured epidermal cell suspension vs. warm trypsinization preparation non-cultured epodermal cell			
	Microneedling + NB-UVB vs. microneedling + topical triamcinolone			
	Follicular unit extraction vs. pucking hair follicle			
	Non-cultured extracted hair follicle outer root sheath cell suspension vs. non-cultured cell suspension			

CAMOUFLAGE THERAPY

	Certainty of evidence			
	Very low	**Low**	**Moderate**	**High**
Interventions	None	Sabgh (herbal formulation) vs. Exuviance (active ingredient is titanium dioxide)	None	None

COMPLEMENTARY THERAPY

	Certainty of evidence			
	Very low	**Low**	**Moderate**	**High**
Interventions	CO2 laser + platelet rich plasma vs. plalelet rich placma	None	Vitilinex (herbal bio-actives) + NB-UVB vs. vitilinex	None
	Platelet rich plasma vs. CO2		Oral compound glycyrrhizin + UVB vs. oral compound glycyrrhizin	
	Monochromatic excimer light + khellin + vitamin E vs. vitamin E		yiqiqubai granule + 308 nm excimer laser vs. yiqiqubai granule	

DEPIGMENTATION

	Certainty of evidence

	Very low	Low	Moderate	High
Interventions	Facial depigmentation vs. extra-facial depigmentation	None	None	None

NON-COMPARATIVE STUDIES (VERY LOW CERTAINY EVIDENCE)

Topical therapies	Ruxolitinib 1.5%
	Ruxolitinib 1.5% cream + optional NB-UVB
Depigmentation therapies	Laser assisted depigmentation (QS laser)
	694-nm QSR laser
	Q-switched Nd:YAG laser at 532-nm wavelength
	Monobenzyl ether of hydroquinone (MBEH)
	Cryotherapy and/or 755nm laser therapy
Systemic therapies	Tofacitinib + NB-UVB
Combination therapies	Tacrolimus 0.03% or tacrolimus 0.1% with NB-UVB
	Minigraft + phototherapy
	Nutritional therapy + topical therapy
	Nutritional therapy + systemic steroid pulse therapy or triamcinolone intralesional injection
	Nutritional therapy + excimer laser
	Nutritional therapy + topical therapy + systemic steroid pulse therapy or triamcinolone intralesional injection
	Nutritional therapy + topical therapy + excimer laser
	Nutritional therapy + systemic steroid pulse therapy or triamcinolone intralesional injection + excimer laser

		Nutritional therapy + topical therapy + systemic steroid pulse therapy or triamcinolone intralesional injection + excimer laser
		Nutritional therapy + epidermal graft
		Methyl prednisolone + NB-UVB
		Methyl prednisolone + topical 0.01% fluticasone ointment
	Surgical therapies	Autologous epidermal transplantation
		Melanocyte-keratinocyte transplantation
		Motorized 0.8-mm micro-punch grafting
		Topical flurouracil 5% needling (26-G needle)
	Skin camouflage therapies	Skin camouflage
		Dihydroxyacetone (DHA) 6%
		Camouflage therapy workshop
		Skin camouflage
	Complementary therapies	Dead sea climatotherapy
		Leeches
		Vitalog (containing 80 mg of *Stachytarpheta cayensensis Vahl* aqueous dried extract)
		Homeopathy
		Nigella satvia seed oil
		Autologous NCES combined with platelet rich fibrin (PRF)
Patient values and preferences	Patients with vitiligo generally do not report physical symptoms as a result of the loss of their pigment but the change in their appearance, the unpredictable progression of the condition contribute in some patients to emotional stress and psychosocial burden. Currently there is no 'cure' for vitiligo, but patients are encouraged by newly emerging oral and topical treatments. Patients are hopeful that a more effective and long-term treatment option will be available to them in the next decade.	

	The following are views, reports, and recommendations, gained from patients' perspectives. These patients' perspectives have been provided from canvassing patients' views in the membership of Vitiligo Support UK and from our patient representatives: **Gaining access to a diagnosis and treatment** Patients report increasing difficulties in accessing treatment in both in primary and secondary care. It is important to explain clearly to your General Practitioner or dermatologist the extent to which your vitiligo is affecting you and your daily work and life, to gain access to a referral or a treatment pathway. Patients' experiences are that, if you are seeking treatment, it is useful to photograph your vitiligo and monitor its progression over a period of 1-3 months. This can provide a clear picture to your GP or dermatologist as to how quickly it is developing. There is a link between thyroid disease and vitiligo. Patients need to be aware of symptoms and their family history of thyroid disease as well as other autoimmune conditions such as pernicious anemia, Addison's disease, atopic dermatitis, and Type I diabetes amongst others. In vitiligo patients, extensive blood tests are usually not required. There is no specific blood test to diagnose vitiligo. If patients are concerned about their risk of autommine diseases or a possible Vitamin D deficiency because of a reduction in their 'incidental exposure' to sun or frequent usage of sunscreen when outdoors, it is recommended that patients discuss this with their GP. The advice of Public Health England is that everyone should supplement with Vitamin D between the months of October to April (https://www.gov.uk/government/news/phe-publishes-new-advice-on-vitamin-d) **Standard Treatments** The first-line treatment, which is usually offered to vitiligo patients by their GP, is a high potency steroid cream. Topical immunomodulators such as tacrolimus and pimecrolimus are often being prescribed by dermatologists only (secondary care).

	Patients often feel that they have to persist in order to get access to secondary care and especially to hospital phototherapy units. Many patients opt for home hand-held or full-body phototherapy devices, as they become increasingly available online. The risks of using these devices unmonitored include phototherapy-associated side effects such as burns, especially of sensitive areas (eyelids and genitals), and skin cancer. It is recommended that patients follow carefully the information leaflet provided by the device's manufacturer and consult their dermatologist. **<u>Covering up your vitiligo</u>** Traditionally, cosmetic camouflage has been the main way of covering up vitiligo patches. The products are gender-neutral and have to be applied on a daily basis. Cosmetic camouflage face-to-face tutorials are available through the charity "Changing Faces". Appointments can either be made online via the Changing Faces https://www.changingfaces.org.uk/skin-camouflage/what-is-the-skin-camouflage-service) or through a referral from a GP or a dermatologist. Other products can also provide a good and long-lasting alternative to covering up if you chose not to use camouflage, and support groups will be able to direct patients further as to which are recommended by users. **<u>Sunscreen</u>** Many vitiligo patients report that their vitiliginous patches burn easily when exposed to sunlight. It is strongy recommended that sunscreen with four-star UV rating and factor 50 SPF need to be applied on vitiligo patches, before leaving going outdoors into the sun. It is important to remember to reapply sunscreen throughout the day and particularly after swimming or sweating heavily and to recognise the limited amount of time you can spend in the sun before sustaining burns on your vitiligo patches. Use shade, clothing and hats, and time out of the sun to reduce your risk. Sunscreens are sometimes available on prescitption for vitiligo patients; however, many Clinical Commissioning Groups have removed sunscreens from their list of prescribable items.
Cost	One systematic review was identified, which aimed to ascertain all economic evidence relating to vitiligo.[201] The systematic review identified only two studies with an economic objective, one study conducted a willingness-to-pay survey in 3319 German vitiligo patients; 1023 of 3319 patients responded and 32.5% stated that they would be willing to make a one-off investment of ≥ €5000202 and the second study used routinely collected data to estimate the annual direct health-care burden cost of treating vitiligo, which was $175 000 000 in 2004.203

	However, both studies did not conduct a full economic evaluation of vitiligo treatments from any perspective (patient, hospital/clinic, healthcare system or society),[202,203] this highlights the lack of cost-effectivness studies for interventions used in vitiligo. **Future Research Recommendation:** A cost-effectiveness analysis of treatments for people with vitiligo within a U.K. healthcare setting.
Other considerations	The GDG agreed on the importance of guidance for the treatment of common mental health conditions and recognition of depression in people with long-term conditions such as vitiligo. The following NICE guidance may be helpful when considering the mental health of people with vitiligo: • Common mental health problems: identification and pathway to care [CG123][204] • Depression in adults: recognition and management [CG90][205] • Depression in adults with a chronic physical health problem: recognition and management [CG91][206] The following tools can be used when assessing a person with a suspected mental health disorder: • The 4-item health questionnaire (PHQ-4) Patient Health Questionnaire-4 (PHQ-4) | QxMD • The 9-item health questionnaire (PHQ-9) https://patient.info/doctor/patient-health-questionnaire-phq-9 • 2-item Gerneralised Anxiety Disorder Scale (GAD-2) Generalized Anxiety Disorder 2-item (GAD-2) - Mental Disorders Screening - National HIV Curriculum (uw.edu) • 7-item Generalised Anxiety Disorder Scale (GAD-7) https://patient.info/doctor/generalised-anxiety-disorder-assessment-gad-7 The following tools for assessing QoL are specific for people with vitiligo: • Vitiligo Specific health related Quality of Life Instrument (VitiQoL)[207] • Vitiligo Impact Patient Scale (VIPs)[198]

	The GDG formulated the following general recommendations for diagnosis and management of people with vitiligo based on practice: **Recommendation GPP:** Undertake a full history for people with vitiligo including the site and type of vitiligo (segmental, non-segmental), disease extent (affected body surface area), disease stability, speed of onset, trigger factors, quality of life, psychological/psychosocial impact, and personal and family history of associated thyroid dysfunction or other autoimmune disease. **Recommednation GPP:** Screen for anti-thyroid antibodies and thyroid function in people with vitiligo (including children) to identify those at high risk of developing autoimmune thyroid disease. **Recommendation GPP:** Discuss with people with vitiligo (including children) the psychosocial impact of living with the condition, emphasizing the relationship between the skin and the mind. **Recommednation GPP:** Refer people with suspected vitiligo to a healthcare professional experienced in managing the condition (secondary care specialist or general physicians with enhanced role, GPwER) if: • the condition is progressing rapidly • there is diagnostic uncertainty • the condition has a significant psychosocial impact • the condition is not responding to topical treatment. **Recommendation ↑↑:** Assess* and monitor the QoL and level of psychological distress associated with living with vitiligo. Assessment tools that can be used include Patient Health Questionnaire 4 (PHQ4)[208,] Patient Health Questionnaire 9 (PHQ9)[209,] Generalized Anxiety Disorder 7 (GAD7)[210,] Dermatology Life Quality Index (DLQI)[211,] and more specifically the vitiligo impact patient scale (VIPs)[198] or Vitiligo specific quality of life (VitiQoL)[207.] **Recommendation GPP:** Provide people with vitiligo (including children) with a patient information leaflet on the condition and prescribed treatments (e.g. British Association of Dermatologists PILs www.skinhealthinfo.org.uk/a-z-conditions-treatments/).

		Recommendation GPP: Consider measuring serum vitamin D levels in people with vitiligo who are avoiding all sun exposure. If levels are reduced or deficient, advise that they may wish to consider taking supplementary vitamin D3 (10-25 micrograms per day) and increasing their intake of foods high in vitamin D, such as oily fish, eggs, meat, fortified margarines, and cereals. **Recommendation GPP:** Monitor the skin of people with vitiligo for treatment response (or rapid progression) via medical photography (digital imaging) taken at the beginning of treatment and at regular intervals of approximately 3-6 months. Alternatively, body surface area (BSA) and area affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com. **Recommendation GPP:** Offer sunscreen with 4* or 5* UVA rating and SPF 50 to people with vitiligo, applied to affected patches and surrounding skin before going outdoors into the sun.
LIST OF RECOMMENDATIONS		
GENERAL RECOMMENDATIONS		
R1	**GPP**	Undertake a full history for people with vitiligo including the site and type of vitiligo (**segmental, non-segmental**), disease extent (affected body surface area), disease stability, speed of onset, trigger factors, quality of life, psychological/psychosocial impact, and personal and family history of associated thyroid dysfunction or other autoimmune disease.
R2	**GPP**	Screen for anti-thyroid antibodies and thyroid function in people with vitiligo (including children) to identify those at high risk of developing autoimmune thyroid disease.
R3	**GPP**	Discuss with people with vitiligo (including children) the psychosocial impact of living with the condition, emphasizing the relationship between the skin and the mind.
R4	**GPP**	Refer people with suspected vitiligo to a healthcare professional experienced in managing the condition (secondary care specialist or general physicians with enhanced role, GPwER) if:

		• the condition is progressing rapidly • there is diagnostic uncertainty • the condition has a significant psychosocial impact • the condition is not responding to topical treatment.
R5	↑↑	Assess* and monitor the QoL and level of psychological distress associated with living with vitiligo. Assessment tools that can be used include Patient Health Questionaire 4 (PHQ4),[208Patient] Health Questionnaire 9 (PHQ9),[209] Generalized Anxiety Disorder 7 (GAD7),[210] Dermatology Life Quality Index (DLQI),[211] and more specifically the vitiligo impact patient scale (VIPs)[198] or Vitiligo specific quality of life (VitiQoL).[207]
R6	**GPP**	Provide people with vitiligo (including children) with a patient information leaflet on the condition and prescribed treatments (e.g. British Association of Dermatologists PILs www.skinhealthinfo.org.uk/a-z-conditions-treatments/).
R7	**GPP**	Consider measuring serum vitamin D levels in people with vitiligo who are avoiding all sun exposure. If levels are reduced or deficient, advise that they may wish to consider taking supplementary vitamin D3 (10-25 micrograms per day) and increasing their intake of foods high in vitamin D, such as oily fish, eggs, meat, fortified margarines and cereals.
R8	**GPP**	Monitor the skin of people with vitiligo for treatment response (or rapid progression) via medical photography (digital imaging) taken at the beginning of treatment and at regular intervals of approximately 3-6 months. Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com.
R9	**GPP**	Offer sunscreen with 4* or 5* UVA rating and SPF 50 to people with vitiligo, applied to affected patches and surrounding skin before going outdoors into the sun.
TOPICAL THERAPIES		
R10	↑↑	Offer a potent or very potent topical corticosteroid once daily to minimize potential side effects to people with vitiligo as the first-line treatment in primary or secondary care, avoid periocular area.

R11	**GPP**	Discuss with people with vitiligo the amount of topical corticosteroids to be used, the site of application, and the safe use of a potent or very potent topical steroid when used correctly.
R12	**↑**	Consider topical tacrolimus 0.1% ointment twice daily in people with facial vitiligo as an alternative to potent or very potent topical corticosteroids.
R13	**↑**	Consider topical tacrolimus 0.1% ointment twice daily **under occlusion** on photo-exposed areas only in people with **non-facial vitiligo** as an alternative to potent or very potent topical corticosteroids.
R14	**GPP**	Consider an intermittent regimen of once daily application of potent or very potent topical corticosteroids with or without topical calcineurin inhibitors (more evidence for tacrolimus), factoring the risks and benefits, in people with vitiligo especially in areas with thinner skin, e.g. periocular region, genital area and skin flexures. Examples of intermittent regimens would include: • 1 week of potent or very potent corticosteroids and at least 1 week off • 1 week of potent or very potent topical corticosteroids alternating with ≥ 1 week of topical calcineurin inhibitor. Topical corticosteroids could be used for longer than 1 week in the intermittent regimen, after consideration of the risks and benefits.
R15	**GPP**	Reassess the use of topical treatments (**R10-R14**) every 3-6 months in people with vitiligo to check for improvement. The use of periodic medical photographs may help assess these changes.
Θ		There is insufficient evidence to recommend topical vitamin D analogues in people with vitiligo.
DEPIGMENTATION THERAPIES		
R16	**GPP**	Consider depigmentation therapies in people with **extensive vitiligo** on visible sites, in whom the condition is having a negative psychological impact. This should be done after adequate psychological assessment and/or intervention. Please refer to the supplementary information document for further details.
SYSTEMIC THERAPIES		

R17	↑	Consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months followed by tapering of the dose by 1 mg/month for a further 3 months in combination with NB-UVB in people with **rapidly progressive vitiligo** to arrest activity of the disease after careful consideration of risks and benefits. (see **R18**)
R18	**GPP**	Consider an equivalent dose of alternative oral corticosteroids in people with **rapidly progressive vitiligo** if betamethasone is not available.
R19	↓↓	Do not offer azathioprine in combination with PUVA (and NB-UVB) to people with vitiligo due to the risk of malignancy.
Θ		There is insufficient evidence to recommend any currently available systemic treatments as monotherapy for people with **stable vitiligo**. However, there is some evidence for their use in combination with other treatments for **rapidly progressive vitiligo** (See **R17 and R18**)
Θ		There is insufficient evidence to recommend minocycline, methotrexate or tofacitinib for people with vitiligo.
LIGHT AND LASER MONO- AND COMBINATION THERAPIES		
R20	↑↑	Offer NB-UVB (whole body or localised, e.g. home-based hand-held) as first-line phototherapy to people with vitiligo who have an inadequate response to topical therapy and/or with extensive or progressive disease. This may be combined with topical calcineurin inhibitor[†] (more evidence for tacrolimus) or potent topical corticosteroid, [‡] for localised sites. Counsel patients on the significant risk of loss of response upon treatment cessation. [†] Prior to combination NB-UVB and topical tacrolimus treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. A shared decision should be made with the person with vitiligo, taking into account other alternatives, the individual's personal and family history of skin cancer risk and the impact of the vitiligo. [‡] The evidence for potent topical corticosteroid is limited. Prior to this combination, consider the risk/benefit ratio of the prolonged use of potent topical corticosteroid.

R21	**GPP**	Inform people with vitiligo who are eligible for NB-UVB of the requirements (depending on local protocols: a pre-therapy assessment, medical photographs taken prior to and during follow-ups 3-6 months, two to three sessions weekly possible for up to 1 year), and the likely response depending on the affected anatomical site (e.g. the face and trunk usually achieve better repigmentation than acral sites). Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented or patients could use personal devices to take photographs if medical photography is not available or not practical. Please refer to vitiligo calculator www.vitiligo-calculator.com.
R22	↑	Only consider PUVA/PUVAsol in adults with vitiligo if treatment with NB-UVB is unavailable or has been ineffective. [§] § For contraindications refer to BAD PUVA guidelines 2016
R23	↑	Consider excimer laser or light in people with **localised vitiligo** in combination with topical calcineurin inhibitors (more evidence for tacrolimus). Prior to treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.
R24	↑	Consider CO2 laser in combination with 5-fluorouracil in adults with **non-segmental vitiligo** on **hands and feet if** other treatments have been ineffective (apply 5-fluorouracil once daily for 7 days per month for 5 months; CO2 laser treatments once a month for 5 months). This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.
Θ		There is insufficient evidence to recommend combination treatment of potent or very potent topical steroid with NB-UVB plus CO2 laser for people with vitiligo.
SURGICAL THERAPIES		
R25	↑	Consider cellular grafting, e.g. blister grafting or cell suspension, in people with **stable**, **segmental,** or **non-segmental** vitiligo that is unresponsive to other treatments, and who remain distressed by the condition. This treatment is not widely available on the NHS but in a limited number of centres with a specialist interest.
Θ		There is insufficient evidence to recommend mini-punch grafting in people with vitiligo.

PSYCHOLOGICAL THERAPIES		
R26	↑↑	Offer* information on self-help (e.g. leaflets, books, websites, apps) to people with vitiligo with mild psychological distress.
R27	↑↑	Offer* referral to psychological services for group or/and individual cognitive behavioural therapy (CBT) to people with vitiligo with moderate-to-severe psychological distress.
SKIN CAMOUFLAGE THERAPIES		
R28	↑	Consider a skin camouflage consultation in people with vitiligo who would like to explore this option.
COMPLEMENTARY THERAPIES		
Θ		There is insufficient evidence to recommend a specific complementary therapy for people with vitiligo.
FUTURE RESEARCH RECOMMENDATIONS		
FRR1		A national registry for people with vitiligo undergoing systemic or light therapy to identify outcomes and safety.
FRR2		A prospective, randomized controlled trial evaluating the safety and efficacy of topical tacrolimus combined with NB-UVB compared with commonly used interventions.
FRR3		A prospective, randomized controlled trial evaluating the safety and efficacy of topical 5-fluorouracil compared with commonly used interventions in adults with vitiligo.
FRR4		Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of oral JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.
FRR5		Prospective, randomized controlled trials are needed to evaluate the safety and efficacy of topical JAK-inhibitors, alone or in combination, compared with commonly used interventions in people with vitiligo.

FRR6	Prospective, randomized controlled trials evaluating the safety and efficacy of CO2 laser for vitiligo compared with commonly used interventions in adults with vitiligo.
FRR7	Prospective randomized controlled trials evaluating the safety and efficacy of afamelanotide compared with commonly used interventions in adults with vitiligo.
FRR8	Prospective randomized controlled trials evaluating the effectiveness of psychological interventions in people with vitiligo.
FRR9	A cost-effectiveness analysis of treatments for people with vitiligo within a U.K. healthcare setting.

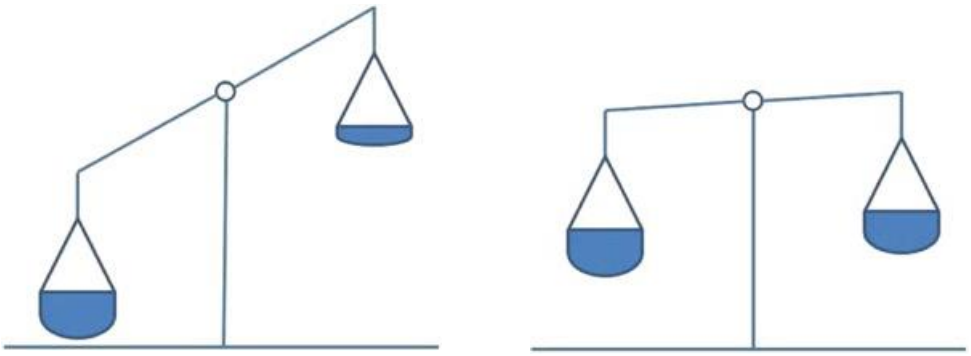
- **Appendix D**)
- Evidence tables of the reviewed literature (Appendices Appendix **E**Appendix **F**Appendix F**: Comparative studies with non-extractable data**Appendix **G**Appendix H**: Narrative findings from non-comparative studies**)
- Forest plot (Appendix B**: Forest plots**)

Recommendations were drafted based on the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms, costs between different courses of action and patient values and preferences. The clinical benefit over harm (clinical effectiveness) focused on the ***critical*** outcomes when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the GDG's, and patient values and preferences), and the confidence the GDG had in the evidence (evidence certainty). The GDG assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical evidence was of poor certainty, conflicting or absent, the GDG drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, practical and economic considerations, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation see *FRRs;* Appendix C).

The GDG considered the appropriate 'strength' of each recommendation. This took into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' (↑↑) in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people (see Figure L.2a) and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms (see Figure L.2b), and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effects and others are not. For clinicians, this indicates the need to consider the pros/cons for the patient in context of the evidence and that variation in practice is expected. In these circumstances, the recommendation is generally weaker (↑), although it may be possible to make stronger recommendations about specific groups of patients, or when experience and expertise in the GDG called for it despite the weaker evidence (e.g. when certain interventions are well established in clinical practice with no recent high-certainty RCTs, or when conducting an RCT would be unethical).

Figure L.2: Illustration for (a) strong and (b) weak recommendations



	(a) Strong recommendations	(b) Weak recommendations
For patients	Most people in this situation would want the recommended course of action and only a small proportion would not	Many people in this situation would want the suggested course of action, but others would not
For clinicians	Most people should receive the intervention	Consider pros/cons for patient in context of the evidence
For quality monitors	Useful as a performance indicator	Poor indicator (variability in practice expected)

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions healthcare professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the words 'Offer', 'Assess', 'Advise', 'Discuss', etc. were used for strong recommendations and 'Consider' for weaker recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care

The main considerations specific to each recommendation are outlined in the LETR table(s) (Appendix C).

Future research recommendations (FRRs)

Where areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future guidance
- ethical and technical feasibility

Validation process

The draft document was made available for a 1-month consultation to all relevant stakeholders identified by the GDG, including healthcare professionals and patient support groups. All comments were reviewed by the GDG and the recommendations were revised if appropriate (for example, in light of important new evidence or other considerations not previously considered by the GDG). Following further review, the finalized version was peer-reviewed by the Clinical Standards Unit of the BAD (which includes the Therapy & Guidelines sub-committee) prior to submission to the British Journal of Dermatology.

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Appendix L: Search strategy

PubMed search carried out on 11.02.2015; 1st top-up on 24.05.16; 2nd top-up on 04.04.2018; 3rd top-up on 20.05.19.

Search no.	Keywords

1	meta-analys* OR “systematic review” OR controlled clinical trials, randomized [MeSH Terms], randomi* controlled trial* OR randomi* control trial* OR RCT* OR non-randomi* controlled trial* OR non-randomi* control trial* OR controlled clinical trial* OR clinical monitor* OR case series OR case report* OR case control* OR open stud* OR cohort stud*
2	vitiligo [MeSH Terms] OR vitiligo OR leucoderma OR leukoderma OR hypopigmentation [MeSH Terms] OR hypopigmentation OR depigmentation
3	1 AND 2
4	therapy OR therapies OR treatment OR management OR intervention* OR immunosuppress*
5	2 AND 4
6	3 OR 5
7	Limit 6 to publications from 01.01.07-20.05.19
8	Limit 7 to English-language publications

MEDLINE & EMBASE search carried out on 11.02.2015; 1st top-up on 24.05.16; 2nd top-up on 04.04.2018; 3rd top-up on 20.05.2019.

Search no.	Keywords
1	meta-analys$2 OR (systematic pre/0 review$1) OR (randomi$3 pre/0 control$3 pre/0 trial$1) OR RCT$1 OR (non-randomi$3 control$3 pre/0 trial$1) OR (control$3 pre/0 clinical pre/0 trial$1) OR (clinical pre/0 monitor$3) OR (case pre/0 series) OR (case pre/0 report$1) OR (case pre/0 control$1) OR (open pre/0 stud$3) OR (cohort pre/0 stud$3)
2	vitiligo [MeSH terms] OR vitiligo [EMB Terms] OR vitiligo OR leukoderma [EMB terms] OR leucoderma OR leukoderma OR hypopigmentation [MeSH Terms] OR hypopigmentation [EMB terms] OR hypopigmentation OR depigmentation
3	1 AND 2
4	therap$3 OR treatment OR management OR intervention$1 OR immunosuppress$3
5	2 AND 4
6	3 OR 5
7	Limit 6 to publications from 01.01.07- 20.05.19
8	Limit 7 to English-language publications

Cochrane main search carried out on 11.02.2015; 1st top-up on 24.05.16; 2nd top-up on 04.04.2018; 3rd top-up on 20.05.2019

Search no.	Keywords
1	vitiligo [expode MeSH terms] OR vitiligo OR leucoderma OR leukoderma OR hypopigmentation [expode MeSH Terms] OR hypopigmentation OR depigmentation
2	Limit 6 to publications from 01.01.07- 20.05.19

Appendix M: Audit standards, data items and data collection

Point 1	
Description	All people with vitiligo should have the type of vitiligo, disease stability, skin type, extent of disease and quality of life documented at initial assessment.
Data items	1. Type of vitiligo. 2. Disease stability. 3. Skin type. 4. Extent of disease. 5. Quality of life.
Collection methodology	Records of 20 consecutive people with vitiligo should be reviewed retrospectively for evidence in clinical notes.
Royal College of Physician Domains	4
Point 2	
Description	All people with vitiligo should undergo a psychological assessment following referral to secondary care.
Data items	1. Psychological assessment following referral to secondary care.
Collection methodology	Records of 20 consecutive people with vitiligo should be reviewed retrospectively for evidence in clinical notes.
Royal College of Physician Domains	2, 4
Point 3	
Description	All people with vitiligo should have thyroid antibody screening.
Data items	1. Thyroid antibody screening.
Collection methodology	Records of 20 consecutive people with vitiligo should be reviewed retrospectively for evidence in clinical notes.
Royal College of Physician Domains	2, 4
Point 4	
Description	All people with vitiligo should be offered a potent topical corticosteroid, if clinically appropriate.
Data items	1. Prescription of a potent topical corticosteroid, if clinically appropriate.
Collection methodology	Records of 20 consecutive people with vitiligo should be reviewed retrospectively for evidence in clinical notes.
Royal College of Physician Domains	2, 4

In 2010, the government published its vision for the NHS "Transparency in Outcomes – a Framework for the NHS". This proposed that 'Process Measures' should be replaced by 'Outcome Measures' forming an NHS Outcome Framework with 5 domains:

1. Preventing people from dying prematurely
2. Enhancing quality of life for people with long-term conditions
3. Helping people recover from episodes of ill health or following injury
4. Ensuring people have a positive experience of care
5. Treating and caring for people in a safe environment and protecting them from avoidable harm

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