Home-based narrowband UVB and topical corticosteroid for active and limited vitiligo: the HI-Light Vitiligo RCT

JM Batchelor[1*]; KS Thomas[1*¥]; P Akram[2]; J Azad[3]; A Bewley[4]; JR Chalmers[1]; ST Cheung[5]; L Duley[6]; V Eleftheriadou[7]; R Ellis[3]; A Ferguson[8]; JMR Goulding[9]; RH Haines[6]; H Hamad[10]; JR Ingram[11]; B Laguda[12]; P Leighton[1]; N Levell[13]; A Makrygeorgou[14]; GD Meakin[6]; A Millington[15]; M Ogboli[16]; A Rajasekaran[17]; JC Ravenscroft[18]; A Rogers[2]; TH Sach[19]; M Santer[5]; J Stainforth[20]; W Tan[6]; S Wahie[21]; J White[6]; ME Whitton[1]; HC Williams[1]; A Wright[22]; AA Montgomery[6]

* Joint first authors

1 Centre of Evidence Based Dermatology, University of Nottingham, UK
2 Department of Medical Physics and Clinical Engineering, Nottingham University Hospitals NHS Trust, Nottingham, UK
3 The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
4 Whipps Cross Hospital and The Royal London Hospital, Barts Health NHS Trust, London, UK
5 Primary Care and Population Sciences, University of Southampton, Southampton, UK
6 Nottingham Clinical Trials Unit, Nottingham, UK
7 Leicester Royal Infirmary, Leicester, UK
8 Royal Derby Hospital and the London Road Community Hospital, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK
9 Solihull Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
10 Cannock Chase Hospital and New Cross Hospital, The Royal Wolverhampton NHS Trust, Wolverhampton, UK
11 Division of Infection and Immunity, Cardiff University, Cardiff, UK
12 Chelsea and Westminster Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
13 Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
14 West Glasgow Ambulatory Care Hospital, NHS Greater Glasgow and Clyde, Glasgow, UK
15 Pharmacy Production Unit, Nottingham University Hospitals NHS Trust, Nottingham, UK
16 Birmingham Children's Hospital, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK
17 Birmingham City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
18 Department of Paediatric Dermatology, Nottingham Children's Hospital, Nottingham University Hospitals NHS Trust, Nottingham, UK
19 Norwich Medical School, University of East Anglia, Norwich, UK
20 York Hospital, York Teaching Hospital NHS Foundation Trust, York, UK
21 University Hospital of North Durham; County Durham and Darlington NHS Foundation Trust, Durham, UK
22 St Luke's Hospital, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK

¥Corresponding Author: Professor Kim S Thomas
Centre of Evidence Based Dermatology, The University of Nottingham,
King's Meadow Campus, Lenton Lane Nottingham, NG7 2NR
Kim.Thomas@Nottingham.ac.uk
+44 (0)115 846 8632

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Abstract

Background: Systematic reviews suggest narrowband UVB (NB-UVB) combined with treatments such as topical corticosteroids (TCSs), may be more effective than monotherapy for vitiligo.

Objective: To explore effectiveness and cost-effectiveness of topical corticosteroid monotherapy compared to a) handheld NB-UVB monotherapy and b) handheld NB-UVB/TCS combination treatment, in localised vitiligo.

Design: Pragmatic, 3-arm, randomised controlled trial with 9 months' treatment and 12 months' follow-up.

Setting: 16 UK hospitals – participants recruited from primary and secondary care and the community.

Participants: Adults and children (aged ≥5 years) with active non-segmental vitiligo affecting ≤10% of body area.

Interventions: TCS (mometasone furoate 0.1% + dummy NB-UVB); NB-UVB (NB-UVB + placebo TCS); combination (TCS + NB-UVB). TCS applied once daily on alternate weeks, and NB-UVB administered every other day in escalating doses, with dose adjustment for erythema. Treatments were home-based.

Main outcome measures: Primary outcome was self-assessed treatment success for a chosen target patch at 9 months ('a lot less noticeable' or 'no longer noticeable' on the Vitiligo Noticeability Scale). Secondary outcomes included: blinded assessment of primary outcome and % repigmentation; onset and maintenance of treatment response; quality of life, side effects, treatment burden and cost-effectiveness (cost per additional successful treatment).

Results: 517 participants were randomised (398 adults / 119 children; 52% male; 57% skin types I to III, 43% IV to VI). At 9 months, 370 (72%) participants provided primary outcome data. Median percentage of NB-UVB treatment days (actual/allocated) was 81% for TCS, 77% for NB-UVB and 74% for combination groups, and for ointment 79% for TCS, 83% for NB-UVB and 77% for combination. Target patch location was head & neck (31%), hands & feet (32%) and rest of the body (37%).

Target patch treatment "success" was 20/119 (17%) for TCS, 27/123 (22%) for NB-UVB and 34/128 (27%) for combination. Combination treatment was superior to TCS: adjusted risk difference 10.9% (95% CI 1.0% to 20.9%; p= 0.032; NNT=10). NB-UVB was not superior to TCS: adjusted risk difference

5.2% (95% CI -4.4% to 14.9%; p= 0.290; NNT=19). Secondary outcomes supported the primary analysis. Quality of life did not differ between the groups. Participants who used the interventions for >75% of expected were more likely to achieve treatment success. Over 40% of participants had lost treatment response after a year with no treatment. Grade 3 or 4 erythema was experienced by 62 (12%) (3 using dummy) and transient skin thinning by 13 (2.5%) participants (2 using placebo). We observed no serious adverse treatment effects. For combination treatment compared to TCS, the unadjusted incremental cost effectiveness ratio was £2,328.56 (adjusted £1,932) per additional successful treatment (from an NHS perspective).

Limitations: Relatively high loss to follow-up limits interpretation of the trial findings, especially during the post-intervention follow-up phase.

Conclusion: Handheld NB-UVB + TCS combination treatment is superior to TCS alone for treatment of localised vitiligo. Combination treatment was relatively safe and well tolerated, but only effective in around a quarter of participants. Whether combination treatment is cost effective or not depends how much decision makers are willing to pay for the benefits observed.

Future work: Development and testing of new vitiligo treatments with a greater treatment response and longer-lasting effects are needed.

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Abbreviations

Word	Abbreviation
AE	Adverse Event
CEBD	Centre for Evidence Based Dermatology
CHU-9D	Child Health Utility 9D
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
DVD	Digital Versatile Disc
(e)CRF	(electronic) Case report form
EAC	Equivalent annual cost
EQ-5D-5L	5-level EuroQol 5-dimensional questionnaire
GP	General practitioner
GRIPP2	Guidance for Reporting Involvement of Patients and the Public
HI-LIGHT	Home Interventions and Light therapy for the treatment of vitiligo
HTA	Health Technology Assessments
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
JAK	Janus Kinase
MED	Minimum Erythemal Dose
MHRA	Medicines and Healthcare products Regulatory Agency
NB-UVB	Narrow band ultraviolet B light
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NNT	Number Needed to Treat
NRES	National Research Ethics Service
PPI	Patient and Public Involvement
PROMs	Patient Reported Outcome measures
PSSRU	Personal Social Services Research Unit.
QALY	Quality-adjusted life year
QP	Qualified Person

RCT	Randomised Controlled Trial
REC	Research ethics committee
SAE	Serious Adverse Event
SD	Standard Deviation
START	Systematic Techniques for Assisting Recruitment to Trials
TCS	Topical corticosteroid
TSC	Trial Steering Committee
UK DCTN	UK Dermatology Clinical Trials Network
VitiQOL	Vitiligo Specific Health Related Quality of Life Instrument
VNS	Vitiligo Noticeability Scale

Scientific Summary

Background

Vitiligo is a skin condition that results in complete loss of pigment. It affects around 0.5-2% of the world's population and can develop at any age. Vitiligo can be distressing for patients, especially when it occurs on exposed areas such as the face and hands.

Current clinical guidelines for the management of vitiligo recommend topical corticosteroids (TCS), narrowband UVB (NB-UVB), topical tacrolimus, and combination treatments, but the evidence base for all treatment approaches is limited.

The HI-Light Vitiligo Trial addresses two priority topics from a James Lind Alliance Priority Setting Partnership that were highlighted as being important to people with vitiligo and healthcare professionals:

1. Which treatment is more effective for vitiligo: steroid creams/ointments or light therapy?

2. How effective is UVB therapy when combined with creams or ointments in treating vitiligo?

Objectives

1. To evaluate the comparative effectiveness and safety of home-based interventions for the management of active, limited vitiligo in adults and children. Comparing:
    - Handheld NB-UVB light with potent TCS (mometasone furoate 0.1% ointment)
    - Combination of handheld NB-UVB light plus potent TCS with potent TCS alone.
2. To assess whether treatment response (if any) is maintained once the interventions are stopped.
3. To compare the cost-effectiveness of the interventions from an National Health Service (NHS) and separately a family perspective.
4. To understand the barriers and facilitators to adoption of these interventions within the UK NHS.

Methods

Study Design

A multicentre, three-arm, parallel group, pragmatic, placebo-controlled randomised controlled trial (RCT), with nested health economic analysis and process evaluation.

Recruitment and Follow-up

Participants were recruited from 16 UK hospitals, with recruitment from primary care, secondary care and community advertising, and were trained to deliver the treatments in their homes.

Treatment was for 9 months with a further 12 months' follow-up, participants attended hospital clinics on two consecutive days at baseline for recruitment and training, and then at 3, 6 and 9 months to assess outcomes. Follow-up to 21 months was by 3-monthly questionnaires.

Eligibility Criteria

Participants were aged 5 years and over, with a diagnosis of non-segmental vitiligo, limited to approximately 10% or less of body surface area, and at least one vitiligo patch that had been active in the last 12 months (self-reported). Participants had to be willing to stop other vitiligo therapies; be able to follow the treatment instructions and comply with safety precautions at home; and be willing and able to give informed (or parental/carer) consent.

People were excluded if they had segmental or universal vitiligo; vitiligo limited solely to areas contra-indicated for treatment with potent TCS; history of skin cancer, radiotherapy use or photosensitivity (based on Minimum Erythemal Dose (MED) test); allergy or contra-indication to mometasone furoate; were pregnant women, breastfeeding or likely to become pregnant during the trial; those on immunosuppressive drugs; involved in another clinical trial; or the investigator thought were unable to use the treatments safely.

Interventions

Participants received a handheld NB-UVB light unit (active or dummy) and either TCS (mometasone furoate 0.1% ointment (Elocon®, Merck, Sharp and Dohme) or placebo ointment (vehicle). Treatments were used for up to 9 months. Participants received face-to-face training, online training and a written handbook of instructions.

At baseline, participants selected a target patch that had been active in the last 12 months and in which they most wanted to see improvement. Participants could select up to two further study patches for treatment, with a maximum of one on each of three anatomical regions (head and neck, hands and feet, and rest of body). Participants could treat additional patches if they wished, but these were not assessed in the study.

Handheld NB-UVB (Dermfix 1000 MX, Dermfix Limited, UK) was used on alternate days. The treatment schedule had a starting dose of 0.05 J/cm2, and increased incrementally. Participants recorded treatment times and side effects in a participant's diary.

TCS or placebo ointment was applied once daily on alternate weeks (1 week on, 1 week off).

Outcomes

Primary outcome

Participant-reported treatment success at the target patch of vitiligo after 9 months of treatment, measured using the Vitiligo Noticeability Scale (VNS). Treatment success was defined as vitiligo being 'a lot less noticeable' or 'no longer noticeable' compared with before treatment.

Secondary outcomes

a) Blinded assessment of treatment success (using VNS) at the target patch by a panel of three blinded assessors with vitiligo using digital images at baseline and 9 months;

b) Participant-reported treatment success for each of the three body regions using the VNS, assessed at 9 months (all assessed patches);

c) Onset of treatment response at the target patch: assessed by investigators using the question "Compared to the start of the study, has there been a change in the vitiligo patch?" Onset of treatment response was defined as 'stayed the same (I.e. not worsened)' or 'improved' as all target patches were active patches at baseline;

d) Percentage repigmentation: for the target patch at 9 months, using digital images assessed by a clinician unaware of treatment allocation (treatment success ≥ 75% repigmentation), plus blinded assessment by investigators at 3, 6 and 9 months;

e) vitiligo-specific and generic quality of life: assessed at end of treatment (9 months) and end of follow-up (21 months);

f) Maintenance of treatment response: assessed by participants for the target patch of vitiligo at 12, 15, 18 and 21 months, using the question "Compared to since you stopped using the study treatments, has there been a change in the vitiligo patch?". Loss of treatment response was defined as a response of "worse" at any time-point;

g) Burden of treatment: time per session for active light treatment and participant-reported treatment burden for TCS and light treatments at 3, 6 or 9 months.

Safety outcomes

Adverse reactions during the treatment phase were recorded. Events of interest were pre-defined as grade 3 or 4 erythema and skin thinning. All serious adverse events were also recorded.

Sample size

The target sample size was 440 participants (assuming 15% of participants allocated TCS alone would achieve treatment success, and to detect a clinically significant absolute difference between groups of 20%, with 2.5% two-sided alpha, 90% power and 15% loss to follow-up). A planned sample size review by the Data Monitoring Committee after 18 months of recruitment recommended extending recruitment to 516 participants.

Randomisation and blinding

Participants were randomised to active TCS plus dummy NB-UVB (TCS only group); active NB-UVB plus placebo ointment (NB-UVB only group); or active TCS ointment plus active NB-UVB (combination group). Randomisation was minimised by recruiting centre, body region of target patch (head and neck, hands and feet or rest of the body) and age (5–16 years or >16 years). Randomisation was via a secure web server created and maintained by the Nottingham Clinical Trials Unit (NCTU) to ensure allocation concealment. A central pharmacy distributed the interventions directly to participants' homes.

Participants, research nurses, principal investigators, members of trial management group and data analysts were blinded to treatment allocation. Due to the unblinding risk from skin erythema after NB-UVB treatment, additional outcome assessments were performed by a panel of three patient assessors (for the primary analysis) and a blinded clinician for the secondary outcome of % repigmentation, using digital images taken at baseline and at 9 months.

Statistical methods

For all analyses, two pre-specified between-group comparisons were made: NB-UVB light versus TCS, and NB-UVB light plus TCS versus TCS.

Primary analysis was by intention-to-treat, and with multiple imputation of missing data. The number and percentage of participants achieving 'treatment success' was reported. Randomised groups were compared using a mixed effects model for binary outcomes, adjusted by recruitment centre, body region of target patch, and age at randomisation. The primary estimate of effect was the difference in the percentage of participants achieving treatment success at 9 months, with 95% CI and p values. We also reported relative differences using risk ratios. Sensitivity analyses were conducted to (i) adjust for any variables with imbalance at baseline, (ii) repeat primary analysis

based on participants with primary outcome data and (iii) investigate the impact of treatment adherence. Planned subgroup analyses were (i) children versus adults); (ii) body region of the target vitiligo patch; (iii) hypomelanotic* patch (an indicator of disease activity): definitely or maybe versus no; (iv) >= 4 years duration of vitiligo versus <4 years. These analyses were conducted by inclusion of appropriate interaction terms in the regression model and were considered as exploratory. An additional post-hoc subgroup analysis explored the impact of skin type (types I to III versus types IV to VI).

Secondary outcomes were analysed by a similar approach, using appropriate regression modelling depending on outcome type.

*It is thought that patches which are hypomelanotic, with poorly defined borders, are more likely to be active patches, and therefore more responsive to treatment. Patches were assessed at the point of randomisation using a Wood's lamp, and designated as hypomelanotic with poorly defined borders (or 'hypomelanotic' for short) or amelanotic with sharply defined borders.

Health economics

A nested health economic analysis explored cost-effectiveness of the interventions from an NHS perspective (primary) and a family perspective (secondary). Assessed using participant self-report of healthcare appointments (number, which professional, and relevance to vitiligo), prescriptions for vitiligo treatments and personal expenses. The base case analysis estimates an incremental cost per additional successful treatment with incremental cost per QALY presented in secondary analyses.

Process evaluation

A mixed-methods process evaluation study was conducted to inform interpretation of trial results and to explore barriers and facilitators to adoption of the interventions within the UK NHS.

Twenty-five trial participants (adults, young people or parents) and 10 commissioners were interviewed (9 interviews); twenty-four recruiting site staff completed an online survey; and, thirteen site staff participated in study-review focus groups.

Interviews and focus group data were analysed thematically using an inductive approach; descriptive statistics were generated for online survey responses. Interview prompts and analysis were informed by an initial programme theory, which proposed how combination treatment might ideally work within the NHS. Data were organised to address three key questions:

- *Is home-based treatment manageable for people with vitiligo;*

- *Should combination treatment be made more widely available;*
- *Could combination treatment be made more widely available in the NHS*?

Results

Between May 2016 and September 2017, 517 participants were randomised (398 adults, 119 children). Primary outcome data were available for 370 (72%) participants. Baseline characteristics were well balanced.

The median percentage of NB-UVB treatment days was 81% for TCS, 77% for NB-UVB and 74% for combination groups, and for ointment 79% for TCS, 83% for NB-UVB and 77% for combination. Just under half of participants used the treatments for over 75% of the expected duration.

Investigators thought that they had become unblinded for 21%, 28% and 27% of participants in the TCS, NB-UVB and combination groups respectively. The percentages of participants who thought that they had become unblinded were 39%, 55% and 44% respectively. Unblinding guesses for NB-UVB were correct approximately 80% of the time, but for TCS the guesses were correct less than half of the time.

For the primary outcome, treatment success using the VNS at 9 months was reported by 20/119 (17%) of those allocated TCS, 27/123 (22%) allocated NB-UVB and 34/128 (27%) allocated combination treatment. The adjusted risk difference between combination treatment and TCS was 10.9% (95% CI 1.0% to 20.9%; p= 0.03), and for NB-UVB compared to TCS 5.2% (95% CI -4.4% to 14.9%; p= 0.29). Corresponding adjusted risk ratios were 1.93 (95% CI 1.02 to 3.68) for combination treatment compared to TCS and 1.44 (0.77 to 2.70) for NB-UVB compared to TCS.

Participants who adhered for ≥75% of expected treatments were more likely to achieve treatment success in the combination group compared with TCS (adjusted odds ratio 2.73 (95% CI 1.24 to 6.02)), but not for UVB compared with TCS (adjusted odds ratio 1.52 (95% CI 0.56 to 4.11)).

Secondary outcomes supported the primary analysis. Treatment success (VNS) based on assessment of digital images by patient reviewers showed similar results but were more likely to suggest benefit from NB-UVB, with evidence of differences in treatment success for both the NB-UVB and the combination groups, compared with TCS.

Percentage repigmentation success rates (≥75% repigmentation) using blinded assessment of digital images, confirmed that combination treatment was better than TCS: 4/119 (3%) for the TCS group, 9/123 (8%) for NB-UVB group and 18/128 (15%) for the combination group.

Quality of life was high at baseline for all groups and showed no between group differences at 9 or 21 months

Overall 94% of participants achieved onset of treatment response by 3-months for all groups (defined as the active target patch having improved or stayed the same (i.e. not worsened)). TCS (40% improved 57% stayed the same); NB-UVB (61% improved, 35% stayed the same) and combination (60% improved, 38% stayed the same).

For participants using active light devices the median treatment time was 20 minutes per treatment session. Participants required just over an hour (mean 70 minutes) of face to face training prior to using the treatment at home.

Burden of treatment was identified as an issue by 42/142 (30%) in the TCS group, 38/140 (27%) in the NB-UVB group and 36/149 (24%) in the combination group, although interpretation is difficult as all three groups used both treatments throughout (either active or dummy/placebo). In general, NB-UVB treatment was more burdensome than treatment with TCS.

Grade 3 or 4 erythema occurred in 62 (12%) participants (3 using dummy), and transient skin thinning in 13 (2.5%) participants (2 using placebo), with no serious adverse treatment effects.

In line with the clinical results, the primary cost effectiveness analysis showed that the unadjusted incremental cost per additional successful treatment was £2,328.56 (adjusted £1,932.35) for combination treatment compared to TCS alone and £4,801.92 (adjusted £3,335.74) for NB-UVB alone compared to TCS alone. Whether combination treatment is considered to offer value for money to the NHS depends on the maximum willingness to pay of decision makers to gain an additional treatment success and there is currently no evidence as to what the level might be.

Process evaluation findings

Process evaluation findings suggest that stakeholders were positive about the role of combination treatment in the management of vitiligo.

Despite being time consuming and (potentially) complex, both participants and healthcare professionals indicated that, with appropriate support, combination treatment could be managed at home. Appropriate training and on-going monitoring, particularly in the early stages of treatment are essential, especially given concerns about potential side-effects associated with the treatments.

Trial participants and healthcare professionals both advocated the broader use of combination treatment in the NHS, with some caveats about which patients might benefit most.

Both healthcare professionals and commissioners recognised that the need for a developed infrastructure (nursing support, medical physics service) might be a barrier to broader NHS provision. Regional clinics might be a possible solution, as might some form of mixed economy approach, where patients purchase light-therapy devices alongside NHS support and training.

Conclusions

Implications for healthcare

Combination treatment with NB-UVB and potent TCS is superior to potent TCS alone, although the benefits are likely to be modest. Combination treatment was relatively safe, well tolerated and cost-effective for people with limited vitiligo that had been active within the last 12 months.

Home-based NB-UVB therapy requires quality control of devices, training and support from healthcare professionals with experience of delivering phototherapy services and is time intensive for patients, but appears to be a useful treatment option for people with localised active vitiligo and provides considerable advantages over hospital NB-UVB therapy, which requires hospital visits 2-3 times per week.

Use of mometasone furoate 0.1% (a potent corticosteroid) as first-line treatment for vitiligo is supported as it achieved treatment success in 1 in 6 individuals and was effective in stopping the spread of active vitiligo patches. It was also found to be safe in both adults and children when used daily on alternate weeks for 9 months.

Treatment effects were lost once interventions were stopped, suggesting that intermittent maintenance therapy is likely to be needed.

These findings require a broad dissemination strategy that includes general practice as well as dermatology services.

Implications for research

Research priorities include:

1. Development and testing of new vitiligo treatments with a greater response and longer-lasting effects.
2. Investigation of treatments suitable for people with widespread vitiligo.
3. Research into different strategies to maintain treatment response once treatments are stopped

4. Further development and validation of outcome instruments to be included in the vitiligo core outcome set, to facilitate combining of trial results in meta-analyses.

Trial registration

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Funding

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Plain English Summary

The HI-Light vitiligo trial aimed to find out whether treating vitiligo at home with a particular type of ultraviolet light (NB-UVB), either by itself or with a steroid ointment, is better than treatment using a steroid ointment on its own.

We enrolled 517 children and adults who had small, recently changing patches of vitiligo into the study. Participants received one of three possible treatment options: steroid ointment (plus dummy light), handheld NB-UVB light (plus placebo ointment) or both treatments used together.

We asked participants to judge how noticeable their target vitiligo patch was after 9 months of treatment. We considered the treatment was successful if the participants' responses were either 'a lot less noticeable' or 'no longer noticeable'.

The results showed that using both treatments together was better than using steroids ointments on its own. Around a quarter of participants (27%) who used both treatments together said that their vitiligo was either 'no longer noticeable' or 'a lot less noticeable' after 9 months of treatment. This compared to 17% of those using steroid ointment on its own and 22% of those using NB-UVB light on its own.

All treatments were able to stop the vitiligo from spreading. Patches on the hand and feet were less likely to respond to treatment than patches on other parts of the body.

The trial found that the vitiligo tended to return once treatments were stopped, so ongoing intermittent treatment may be needed to maintain treatment response.

The treatments were found to be relatively safe and easy to use, but light treatment required a considerable time commitment (approximately 20 minutes per session, 2 to 3 times per week).

This trial showed that using steroid ointment and NB-UVB light together is likely to be better than steroid ointment alone, for people with small patches of vitiligo. Steroid ointment alone can still be

effective for some people and remains a useful treatment that is able to stop vitiligo from spreading. The challenge is to make handheld NB-UVB light treatment available as normal care within the NHS for people with vitiligo.

Chapter 1: Introduction

1.1 Background

Vitiligo is an acquired, chronic skin condition, which causes loss of skin pigmentation. This leads to milky white, well-demarcated non-scaly patches on the affected skin and/or mucosal surfaces. The depigmentation seen in vitiligo is caused by destruction of pigment cells (melanocytes), although the precise cause of this is still unclear. Vitiligo is considered to be a multi-factorial disease [1-6]. In the light of recent genome-wide studies, there is growing evidence that vitiligo has, at least in part, an autoimmune basis, and this is a target for future treatments, although these are still in development [7].

Vitiligo affects around 0.5-2% of the world's population. Vitiligo can develop at any age but most commonly occurs between the age of 10 and 30 years [8-12]. Whilst there is equal prevalence of vitiligo in adults and children of both sexes, females tend to seek treatment more often, possibly due to the greater social stigma experienced by women and girls with the condition [10, 13].

Vitiligo may be segmental (affecting one specific area of skin) but is commonly non-segmental (affecting multiple, symmetrically-distributed areas). The most commonly affected sites are the face, neck and trunk [14]. The cosmetic disfigurement of this seemingly inconsequential skin disease has a major impact on quality of life [15]. It can be particularly distressing for people with darker skin types, especially if the vitiligo occurs on highly visible sites, such as the face and hands[16]. People with vitiligo can experience a number of psychological problems such as depression and anxiety, which may lead to low self-esteem and social isolation [15-18].

Current clinical guidelines for the diagnosis and management of vitiligo recommend narrowband ultraviolet light B (NB-UVB), topical tacrolimus, topical corticosteroids (TCSs) and combination treatments [19, 20].

1.2 Rationale for the HI-light Vitiligo trial

Importance of the topic to patients and healthcare practitioners

A James Lind Alliance Priority Setting Partnership identified priority topics for future vitiligo research, which were important to patients and healthcare practitioners [21]. The HI-Light Vitiligo Trial has been designed to address two of the priority topics:

1. Which treatment is more effective for vitiligo: steroid creams/ointments or light therapy?

2. How effective is UVB therapy when combined with creams or ointments in treating vitiligo?

The Priority Setting Partnership also highlighted the importance of testing vitiligo treatments in children; so the HI-Light Vitiligo Trial recruited both children and adults.

1.3 Existing Evidence

A 2010 Cochrane systematic review looking at interventions for the treatment of vitiligo identified 57 trials covering 68 different treatment options [22]. The quality of the trials included in the review was generally poor, making it difficult to make firm recommendations. The use of NB-UVB light therapy was generally supported, and the combination of light treatment with other active interventions appeared to be more effective than monotherapies. However, due to heterogeneity of trial designs, optimal dosing and treatment regimen for NB-UVB could not be established [23]. In 2016 the Cochrane review was updated, and covered 96 trials, none of which provided evidence that was of sufficient quality to alter these overall conclusions.

When the HI-Light Vitiligo trial was first proposed in 2010, the only randomised controlled trial (RCT) that had been conducted to assess the use of hand-held NB-UVB devices for the treatment of vitiligo was the pilot study to the main HI-Light Vitiligo Trial [24]. This demonstrated that the devices were safe and well tolerated when used to treat children and adults at home, and that people with vitiligo were keen to take part in a trial of home-based NB-UVB.

Following this pilot trial, other studies have suggested the efficacy of hand-held NB-UVB devices for vitiligo, including in children, but the studies have been small or retrospective [25, 26], making it difficult to draw firm conclusions.

1.4 Importance of assessing the use of hand-held NB-UVB devices at home

In the UK, NB-UVB treatment is delivered almost exclusively in secondary care, requiring regular hospital visits. NB-UVB is usually reserved for people with widespread vitiligo, because most dermatology services are only equipped with large, full-body NB-UVB units [19].

There are various devices available for the administration of NB-UVB treatments at home, which avoids the need for hospital visits. Some dermatology departments in the UK now supply home NB-UVB units (large machines that look like portable sunbeds for treating large areas of skin) for use by patients with eczema and psoriasis. Early reports suggest that these are well tolerated and effective[27-30].

When treating vitiligo, the choice of the NB-UVB device is usually based on the extent and anatomical location of the vitiligo; limited areas of vitiligo can be treated with a small, hand-held NB-UVB devices [31].

There are several potential benefits of using hand-held NB-UVB devices for treating early, limited vitiligo:

- reduction in attendance at hospital and associated time and travel costs for patients
- only treating involved areas, thus sparing uninvolved skin
- when more extensive whole-body phototherapy is not indicated, NB-UVB treatment of vitiligo can still be used
- low cost of the devices relative to expensive, whole body units

Should a hand-held device prove to be effective and safe for the treatment of vitiligo, this could be an important addition to the treatment options available to people with limited vitiligo in the early stages of the condition, or for those wishing to treat only specific patches.

1.5 Importance of treating early vitiligo

Clinical studies have suggested that treatment of vitiligo in its early stages is more likely to be beneficial than treatment of longstanding vitiligo [25, 32].

For this reason, participants in the HI-Light Vitiligo Trial were required to have at least one patch of vitiligo that changed in the last 12 months (see further details in Section 2.4).

1.6 Patient reported outcome measures

A survey and systematic review of the outcome measures used in previous vitiligo trials, suggested that patients' and clinicians' may have disparate views regarding which outcomes are most important in evaluating treatment response for vitiligo [33].

An international e-Delphi consensus exercise has established core outcome domains for future vitiligo trials.[34] Outcomes that should be measured in all future vitiligo trials include:

- Repigmentation
- Cosmetic acceptability of treatment response
- Maintenance of gained repigmentation
- Cessation of spread

- Quality of Life
- Burden of treatment
- Safety

The HI-Light trial will assess all of these core outcome domains. The core outcome domains include important patient reported outcome measures, including the cosmetic acceptability of treatment response. Prior to recruiting participants to the HI-Light Vitiligo Trial, we developed a new patient-reported outcome measure to assess this domain: the Vitiligo Noticeability Scale (VNS). This instrument has been recommended for use within the core outcome set[35], and has been used as the primary outcome measure for the trial.

The VNS was co-produced with vitiligo patients, using surveys and focus group work to agree the construct of interest and to develop a preliminary version of the instrument. The VNS measures how 'noticeable' the patient thinks their vitiligo is after treatment, using a 5-point scale, with treatment success represented by response options 4 or 5 ("a lot less noticeable" or "no longer noticeable").

1.7 NIHR HTA funding call

In view of the limited evidence for home-based NB-UVB for vitiligo, the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme issued a funding call and subsequently commissioned the HI-Light Vitiligo Trial. The HI-Light Vitiligo Trial is the first large-scale multi-centre, pragmatic RCT to evaluate the use of TCS and NB-UVB at home.

The trial includes a nested cost-effectiveness analysis and a mixed methods process evaluation to explore the views of patients and healthcare professionals on the trial treatments and the potential barriers and facilitators to safe and effective use of the trial treatments within the National Health Service (NHS).

Chapter 2: Methods

The full trial protocol is available on the NIHR project page, and a summary protocol published[36]. CONSORT guidelines have been followed for the analysis and reporting.

2.1 Trial Objectives

1. To evaluate the comparative effectiveness and safety of home-based interventions for the management of active, limited vitiligo in adults and children. Comparing:
   - Handheld NB-UVB light with potent TCS (mometasone furoate 0.1% ointment)
   - Combination of handheld NB-UVB light plus potent TCS with potent TCS alone.
2. To assess whether treatment response (if any) is maintained once the interventions are stopped.
3. To compare the cost-effectiveness of the interventions from an National Health Service (NHS) and family perspective.
4. To understand the barriers and facilitators to adoption of these interventions within the UK NHS.

2.2 Trial Design

The HI-Light trial was a multi-centre, three –arm, parallel group, pragmatic, placebo-controlled RCT. The trial recruited adults (≥ aged 16 years) and children (≥5 to 15 years) with early or limited vitiligo (defined as a coverage of approximately 10% or less of the body surface area).

Trial treatments were administered at home by the participant, with or without assistance from a relative/carer. Participants were initially followed-up in secondary care at 3 and 6 months, and finally at 9 months where the primary outcome was assessed. Long-term follow-up continued for a further 12 months, with online or postal questionnaires completed at 12, 15, 18 and 21 months (See Figure 1)

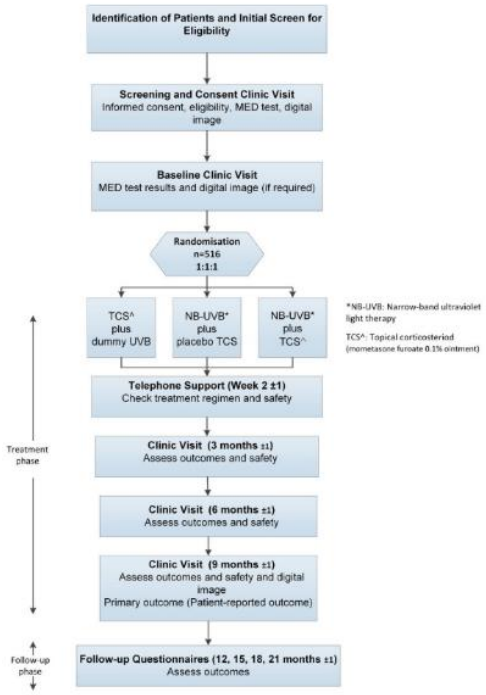

Figure 1 HI-light trial flowchart

The trial included a mixed-methods process evaluation and a health economic analysis.

The study was approved by Health Research Authority East Midlands – Derby Ethics Committee (reference number 14/EM/1173) and by the local research and development department for each participating site prior to recruitment commencing. The trial was registered on Current Controlled Trials prior to start of recruitment (ISRCTN17160087). Subsequent changes to the protocol are summarised (Table 1)

Table 1 Summary of protocol amendments

Protocol version	Date	Summary of changes
2.0	11-Mar-2015	Added details of the MRC Systematic Techniques for Assisting Recruitment to Trials (START) sub-study

3.0	30-Sep-2015	Clarified inclusion and exclusion criteria; added more details about training participants to use trial treatments; procedures clarified for digital images outcome analyses; changes to adverse events (AE) handling for erythema (grade 1 and 2 are not AE, but expected reactions); amendment of pre-specified subgroup analysis to remove a comparison of active and inactive patches (as by definition all target patches will be active); addition of a subgroup analysis evaluating response of target patch by region of the body.
4.0	03-Mar-2017	Added details of the nested process evaluation; updates to the safety handling section; introduction of an online automated blind-break procedure; change to sample size following sample size review by the Data Monitoring Committee (DMC).
5.0	18-Jan-2018	Amendment to reflect the fact that, due to trial timelines, some participants would not receive the full 12 month follow-up but would receive quality of life questionnaires and study feedback questions; updates to statistical analyses section to reflect the statistical analysis plan; addition of output testing of NV-UVB devices after end of treatment phase.

2.3 Trial Setting

Participants were identified when they attended secondary care dermatology clinics, or when they responded to mailshots sent out from general practices. Some participants self-referred, in response to community advertising and trial publicity. A number of patient information sheets were used in the trial, depending on the age of the potential participant.

Recruitment took place at 16 UK sites, details of which are in the Acknowledgements section of this report.

2.4 Participants

Patients were considered for entry into the trial if the following criteria were met:

- Age 5 years or over with a diagnosis of non-segmental vitiligo confirmed by a dermatologist.
- Vitiligo limited to approximately 10% or less of body surface area, with at least one patch reported by the participant to have been active in the last 12 months.
- No other active therapy for vitiligo (or willing to stop current treatment; no washout period required).

- Able to administer the interventions safely at home.
- Able and willing to give informed consent (or parental/guardian consent in the case of children).

In addition, patients were not entered into the trial if any of the following exclusions applied:

- Other types of vitiligo (e.g. segmental or universal vitiligo).
- Patients with vitiligo limited to areas of the body for which NB-UVB light treatment or potent TCS would be inappropriate (e.g. around the genitals).
- History of skin cancer (ever).
- History of radiotherapy use (ever).
- Photosensitivity (e.g. lupus, polymorphic light eruption, solar urticaria, chronic actinic dermatitis, actinic prurigo, porphyria or other photosensitivity disorders).
- Pregnant or breastfeeding women.
- Current use of immunosuppressive or immune modifying drugs (e.g. ciclosporin, azathioprine, mycophenolate mofetil, methotrexate).
- Allergy or contraindication to mometasone furoate or its components.
- Current participation in another clinical trial or intervention study.
- Marked evidence of Koebner phenomenon in the vitiligo (with the condition spreading extensively at the site of skin injury).

Informed Consent

Written informed consent was obtained from each participant (or parent/carer in the case of children) prior to any trial procedures being carried out. Children provided assent as well, if they wished to. Separate written consent was obtained for participation in the process evaluation, supported by a separate age-appropriate information sheet.

2.5 Randomisation and blinding

Randomisation was carried out via a secure web-based server created and maintained by Nottingham Clinical Trials Unit (NCTU). Randomisation was minimised by recruiting centre, body region of target patch (head and neck, hands and feet or rest of body) and age (5-16 years or >16 years).

Participants were randomised to one of three treatment groups in a ratio of 1:1:1 as follows:

- TCS ointment plus dummy NB-UVB light (TCS only);
- Placebo (vehicle) ointment plus NB-UVB light (NB-UVB only);

- TCS ointment plus NB-UVB light (combination treatment).

After completing training in the in use of the trial interventions, undergoing a Minimum Erythemal Dose (MED) test and having photographs taken of the patches of vitiligo to be assessed in the trial, participants were randomised by staff at the recruiting hospital via a secure web-based server created and maintained by NCTU.

Participants, research nurses, principal investigators, members of trial management group and data analysts were blinded to treatment allocation. The Senior Data Manager at NCTU (who created the randomisation schedule), medical physics staff (responsible for the testing of NB-UVB devices prior to distribution) and NCTU Quality Assurance staff (responsible for the blinding of NB-UVB devices) were all aware of the dummy/active nature of each device or ointment.

Whilst every effort was made to ensure that blinding of trial interventions was maintained, and interventions were identical, there was a risk of blinding being compromised due to the nature of the treatments and their known side effect profile (in particular, erythema from NB-UVB treatment). Given this risk of unblinding, the following measures were taken to limit the impact on trial results:

I. Information provided to participants emphasised that all participants received at least one active treatment for their vitiligo, reducing the risk of detection bias due to lack of treatment response.
II. Noticeability of vitiligo was assessed using the VNS by an independent panel of three people with vitiligo, all of whom were blinded, using images taken at baseline and at 9 months. These data are presented as a secondary outcome.

At the end of the treatment phase (9 months), participants and investigators were asked if they believed that they had become unblinded, and if so, to what treatments they thought had been allocated. These data were used to support the interpretation of trial results.

2.6 Interventions

Topical Therapy

Potent topical corticosteroid

Mometasone furoate 0.1% w/w ointment (Elocon® 0.1% Ointment, Merck Sharp & Dohme, Hertford), a potent corticosteroid used once daily, has been recommended in the European Clinical Guidelines for the management of vitiligo [37]. In order to minimise the risk of adverse reactions, the Guidelines recommend a discontinuous regimen involving periods of use followed by break periods. Possible adverse reactions to mometasone furoate 0.1%, as listed in the Summary of Product

Characteristics[38], include: infection, folliculitis, paraesthesia, burning sensation, contact dermatitis, skin hypopigmentation, hypertrichosis, skin striae, acneiform dermatitis, skin atrophy, pruritus, application site pain and visual disturbance. Participants were advised to stop use of the ointment if they noticed any side effects and to contact the local research team for review and advice on when to restart treatment.

Vehicle ointment

The vehicle ointment was white soft paraffin (and inert ointment) present in the base of mometasone furoate. Expected side effects from this treatment were minimal.

Treatment regimen

To reduce the risk of side effects, topical therapy was applied as a thin layer to the affected patches of skin only on alternate weeks (1 week on, 1 week off), for a period of 9 months. In order to mitigate the risk of interaction between ointment and light therapy, participants were instructed to wait for at least 2 hours following light therapy before applying the ointment.

Light Therapy

NB-UVB Device

Several brands of NB-UVB units are CE marked for use in treating vitiligo and other skin conditions and are suitable for use at home. Dermfix 1000 MX units were used in the HI-Light trial, as guided by initial feasibility work[24].

Known adverse reactions to NB-UVB light therapy include: erythema, blistering, burns, pruritus, perilesional hyperpigmentation, hypersensitivity reactions, cold sores and dry skin. Potential long-term risks include skin ageing and increased risk of skin cancer (although the latter is thought to be very low)[39, 40]. Side effects can be reduced by appropriate use of the device.

Dummy Device

The dummy light therapy device was identical to the active device, with the exception that a specially designed spacer comb, identical to that found on the active device, was used to block the transmission of NB-UVB light to the skin. The ‘spacer comb’ for the dummy devices was designed by the device manufacturer to be identical in appearance to the standard spacer comb in the normal devices. These dummy spacer combs filtered out UVB without changing the spectrum of visible light emitted by the device, so that when the dummy devices were used, they would look and feel just like active devices.

Active and dummy devices were tracked using manufacturer's serial numbers. Experience from our pilot trial has shown that the use of a dummy device is acceptable to patients and is effective in blocking the NB-UVB radiation.[24]

There are no known side effects of the dummy NB-UVB devices.

Quality control prior to distribution

All light therapy devices (both active and dummy) were tested for safety and UV output by the Medical Physics Department at Nottingham University Hospitals NHS Trust prior to distribution to participants (See Chapter 7: Device Testing). Any device found to have an output that was ±20% of the expected mean output, or a dummy device testing positive for any NB-UVB emission, was returned to the manufacturer. Any device that was damaged or ceased to function during the treatment phase was replaced with a new unit.

Treatment Regimen

Although NB-UVB (UV radiation wavelengths of 311–312 nanometres) is now the most common form of light therapy used to treat skin conditions, many gaps remain in knowledge about its use. In a 2016 paper[23], Madigan *et al* published a list of 12 key questions regarding the use of NB-UVB for generalised vitiligo. How each of these questions has been addressed within the context of the HI-Light trial is presented in Table 2.

Table 2 Key questions regarding the use of NB-UVB for generalised vitiligo (adapted from Madigan *et al*)

Question		**Strategy tested in the HI-Light Vitiligo Trial**
1	What is the optimal weekly frequency of NB-UVB treatment?	HI-Light Trial: every other day (3–4 times weekly).
		Rationale: this is the most commonly used treatment regimen in the UK.
2	With regard to initial dosing, which strategy should ideally be employed?	HI-Light Trial: all participants started on the same low dose, 0.05 J/cm^2.
		Rationale: MED test was carried out before treatment, but only to identify any undiagnosed cases of photosensitivity. Starting at a fixed low dose, to minimise the risk of symptomatic erythema, was felt to be safer for home delivery of NB-UVB.
3	At subsequent treatments, what increments should be used for dose escalation in the absence of perceptible erythema?	HI-Light Trial: 10% dosing increase after each treatment not followed by erythema.
		Rationale: this reflects typical clinical practice in UK phototherapy services
4	What is the maximum acceptable dose to be given in a single treatment?	HI-Light Trial: maximum dose in the trial is 2.81 J/cm^2.
		Rationale: this reflects typical clinical practice in UK phototherapy services.
5	What is the ideal practice for dose adjustment following symptomatic erythema?	HI-Light Trial: patient self-adjustment for grades 1 and 2 erythema (according to flow chart in patient handbook) and investigator adjusted dosing for grades 3 and 4.
		Rationale: the upwards and downwards dosing used in the trial reflects the clinical practice of most UK phototherapy services.

6	How should the protocol be adjusted for missed doses?	HI-Light Trial: varies in function of number of missed treatments. 1 or 2 missed: go back one step on treatment schedule; 3 missed: go back two steps on treatment schedule; 4–6 missed: 50% of last dose; 6+ missed: restart treatment schedule from beginning. **Rationale**: this conservative approach ensured that participants who missed a lot of doses were not at risk of symptomatic erythema when they restarted treatment.
7	How should a 'course' of NB-UVB therapy be defined? (i.e. at what interval should further exposure be reassessed?)	*Not directly applicable within the scope of the trial.*
8	What is the maximum number of exposures allowable for patients with vitiligo, given the potential risk of carcinogenesis with NB-UVB?	*Not directly applicable within the scope of the trial.* Participants in the trial only treated limited areas of skin and the total number of treatments was less than the current maximum recommended number of treatments.
9	Should dosing strategies differ when treating children with vitiligo?	HI-Light Trial: children were treated in the same way as adults. Parents were given the choice of what patches they were comfortable treating, and could opt out of treating sensitive areas if they wished to do so. **Rationale**: the home-based treatment is more flexible than hospital-based full-body treatment, so it is possible for children to be treated in the same way as adults.

10	Should shielding of sensitive structures (eyelids, areolas and genitals) be a universal requirement, or is it safe to expose these areas if affected by vitiligo?	HI-Light Trial: the trial excluded treatment of vitiligo in the genital region. Other sensitive areas could be treated if they were affected by vitiligo, but would not otherwise be exposed to NB-UVB due to the localised nature of treatment using a hand-held device. If treating the eyes, patients were advised to seek assistance from someone else so that they could keep their eyes closed during treatment, thus reducing the risk of accidental exposure during treatment.
11	What is the most accurate definition of treatment unresponsiveness?	HI-Light Trial: responsiveness to treatment was defined by patient report using the question, 'Compared with the start of the study, has there been a change in the vitiligo patch?'
12	How frequently should patients with vitiligo undergo surveillance following completion of a NB-UVB treatment protocol for both signs of relapse and adverse events? Is there a role for phototherapy in maintenance following repigmentation?	HI-Light Trial: long-term treatment response was assessed 3-monthly for 1 year following completion of NB-UVB treatment. The trial was not designed to evaluate the use of intermittent treatment for maintenance of response. Long-term adverse events were not specifically collected in the trial. **Rationale**: patients are particularly interested in how long treatment response might last and this is now a core outcome domain for vitiligo clinical trials.

Prior to randomisation, all participants received an MED test, to ensure eligibility for the trial. Results of the MED test were not used to determine starting dose of the light therapy, but instead to ensure that the participant did not have any undiagnosed photosensitivity disorder. All participants follow a predefined treatment schedule for the light treatment, with a starting dose of 0.05 J/cm^2 (see Table 3).

Table 3 Summary of Instructions for adjusting light therapy treatment schedule and dosing

Situation	What to Do
No erythema or side effects after last treatment	Increase dose by one step for the next treatment.
Erythema or Overdose	
Grade 1 erythema after last treatment	Go back one step on treatment schedule for next treatment
Grade 2 erythema after last treatment	Skip next scheduled treatment. Go back one step on treatment schedule for following treatment.
Grade 3 erythema or 4 erythema after last treatment	Apply thick layer of trial ointment and contact local research team or local on-call dermatologist. Treatment to resume only on advice of local research team.
Light Overdose (used for 20% longer or more than intended treatment time)	Apply thick layer of trial ointment and seek medical attention (prescription for clobetasol propionate 0.05% twice a day for 2-3 days required). Treatment to resume only on advice of local research team.
Missed Treatments	
One or two missed treatments	At next session, go back one step on treatment schedule.
Three missed treatments	At next session, go back two steps on treatment schedule.
Four or more missed treatments	Contact local research team for advice on new starting dose.
Side Effects	
Itchy or dry skin	Apply moisturiser 3-4 times a day, but not within 2 hours before light treatment. Continue treatments as normal.
Tan around edges	This is normal. Continue treatments as normal.
Rash	Stop treatment immediately and seek medical advice. Treatment to resume only on advice of local research team.

Cold sore	Stop light treatment until the cold sore has healed. Adjust next treatment time according to missed treatment advice.

Storage and distribution of trial treatments

Following quality control assessments (light devices) or Qualified Person (QP) release (ointment), blinded light devices and ointment tubes were dispatched to a central distribution centre (Mawdsleys, Doncaster, UK) for storage. On randomisation of a participant by the trial investigator/nurse, the distribution centre was notified of the container numbers of ointment and the device to be allocated to that participant via a web-based system. Trial treatments were then sent directly to the participant's home following check and further QP release.

Training in use of interventions – 'train the trainer'

As a part of the trial Site Initiation training, trial investigators/nurses were given in-depth training in the administering of trial interventions.

Before randomisation, all participants were trained by the site investigator/nurse in how to apply the ointment, including guidance on avoiding application to the eyelids (if less than 1cm away from the eyelid margin) and sensitive body sites such as the genital area. In addition, participants received training in the correct use of the light therapy devices. Training also covered how to record treatment sessions using the trial handbook, how to follow the trial treatment schedule and how to manage adverse reactions. Participants were given either a DVD or electronic link allowing them to access a specifically designed training video at home, if they wished to revisit the training at any time. Written instructions were also included in the trial handbook. Any potential participant considered unable to follow the treatment regimen safely was excluded from the trial.

Participants received a telephone call from the research nurse 2 weeks post-randomisation to check how they were getting on with the trial interventions and to confirm their understanding of treatment usage and completion of the treatment diaries. Additional training on use of either treatment was provided to the participants at this time point (over the telephone or face-to-face), if deemed necessary.

Choice of vitiligo patch for treatment

During the baseline clinic appointment, participants were asked to select up to three patches of their vitiligo to be assessed as a part of the trial, one from each of three anatomical regions (head and neck, hands and feet and rest of body), although they were permitted to treat as many patches as

they liked throughout the treatment phase. As an aide-mémoire for future appointments, investigators/nurses were encouraged to draw the patches chosen for assessment on 'manikin drawings' within the CRF workbook. Of the three patches selected for assessment, participants chose one patch that they would most like to see an improvement in to be used as the target patch for the trial.

The target patch had to be one that the participant thought had been active in the past 12 months. Previous studies had suggested that patches which are hypomelanotic, with poorly defined borders, are more likely to be active patches, and therefore more responsive to treatment.[41] Patches were assessed at the point of randomisation using a Wood's lamp, and designated as hypomelanotic with poorly defined borders (or 'hypomelanotic' for short) or amelanotic with sharply defined borders (Table 5).

Vitiligo is known to respond differently at different body sites, with the face and neck being more likely to respond to treatment than the hands and feet[42]. Training material provided to recruitment centres advised investigators / nurses to inform participants that patches on the hands and feet may be more difficult to treat so they may wish to choose a target patch from one of the other body regions.

Adherence

Participants used a treatment diary as an aide-mémoire throughout the treatment phase of the trial. Participants were encouraged to record each treatment session (both for ointment and for light therapy) in the treatment diary, along with any additional comments (such as experienced adverse reactions). Treatment diaries were reviewed by investigators/nurses at clinic appointments at 3 and 6 months in order to assess the participants' understanding of the treatment regimen, to encourage adherence and to identify adverse events and any potential additional training requirements.

Summary data obtained from the treatment diaries was used to assess adherence to the treatment regime.

Adherence will be expressed as a percentage, calculated by dividing the total number of treatment sessions reported by the participant by the total number of expected sessions from randomisation to 9 month follow up. The calculation will account for additional factors: 1) non-treatment session expected due to erythema; 2) discontinued treatment due to full repigmentation (adherence should be considered as 100% from the point where they achieved full repigmentation); 3) discontinued treatment for any other reasons (adherence will be 0% from the point of reported discontinuation. Reported use up to this point will be used for calculation).

Concomitant medications

The risk of photosensitivity reaction from NB-UVB light in patients on medications is low, and no change to existing medications was required at the onset of the trial. Participants were advised at the start of the trial that such reactions can sometimes occur, and that they should contact a member of the research team if they developed a persistent rash during the treatment period. Any new medications that were started during the trial were documented on the Case Report Form and also in the participant's medical records at each visit (3, 6 and 9 months), and any medications known to cause photosensitivity were assessed alongside reported adverse reactions as a part of the safety profile of the trial.

Since NB-UVB light is a form of radiation, participants were advised to avoid exposure to other forms of UV exposure during the treatment phase of the trial, including excessive exposure to sunlight.

Patients were only eligible to take part in the trial if they were not using, or were willing to stop using, active therapy for vitiligo. Participants were asked to refrain from using any active treatments for their vitiligo throughout the treatment and long-term follow-up phase, to allow the duration of any treatment effect to be evaluated.

Treatment modifications following adverse events

Having been trained in recognising adverse events, participants were instructed to record any events in their treatment diaries and to contact their recruiting centre if they experienced events of concern, or a serious adverse event (whether they felt it was related to trial treatment or not). For treatment-related side effects, or drug-induced photosensitivity, the site research team provided telephone advice or arranged for a dermatology consultation, as necessary. If required, the research nurse or dermatologist suggested treatment modification, including reduction or suspension (temporary or permanent) of either TCS or light therapy. An appointment was scheduled for a dermatologist to review side effects if deemed necessary, in particular for reported episodes of skin thinning or for more severe episodes of erythema.

In case of a medical emergency where an active treatment of the ointment or the device would need to be stopped, investigators and research nurses were advised to assume that both interventions were active. If knowledge of a participant's allocation was necessary, the local investigator was able to access a 24-hour online blind-break system held by NCTU.

2.7 Outcomes

Primary Outcome

Participant-reported treatment success at 9 months.

Assessed for each participant at 9 months (end of treatment phase) at the target patch. Treatment success was defined as the participant reporting that their vitiligo was either 'a lot less noticeable' or 'no longer noticeable' in response to the question 'Compared with the start of the study, how noticeable is the vitiligo now?', using the previously validated VNS [43].

Secondary Outcomes

1. VNS treatment success by blinded review of digital images at 9 months

Assessed at 9 months at the target patch by three independent patient reviewers using digital images from trial participants and using the same question for the primary outcome. Treatment success was derived from the score given by the majority of the 3 blinded reviewers.

2. Participant-reported treatment success by body region:

Assessed at 9 months, measured using the VNS and analysed by body region (A, B and C). Each participant assessed up to 3 assessed patches from 3 different body regions, including the one chosen as the target patch. During the no-treatment follow-up phase, the same question was used at 12, 15, 18 and 21 months, to assess long-term patient reported noticeability for each body region.

3. Onset of treatment response:

Investigator-assessed onset of treatment response (including cessation of spread) for the target patch. To be assessed at 3, 6 and 9 months using the following question: "Compared to the start of the study, has there been a change in the vitiligo patch?"

- Stayed the same (not worsened)
- Improved
- Got worse

A treatment response was considered to have occurred if the response given was "stayed the same" or "improved". Analyses for this secondary outcome used investigator-assessed responses because they were more likely to remain unblinded than the participants.

4. Maintenance of treatment response:

Participant-assessed maintenance of treatment response (including cessation of spread) for the target patch. This was assessed at 12, 15, 18 and 21 months, to assess long-term patient reported

noticeability using the following question: “Compared to since you stopped using the study treatments, has there been a change in the vitiligo patch?”

- Improved
- Stayed the same
- Got worse

Loss of maintenance of treatment response was defined as “*got worse”*.

5. Percentage repigmentation at 9 months:

Percentage repigmentation was assessed at 9 months by a blinded independent dermatologist using digital images taken at baseline and at 9 months for the target patch. Investigator assessment of percentage repigmentation was also conducted at 3. 6 and 9 months.

6. Quality of life at end of treatment (9 months) and end of follow-up (21 months).
    - VitiQOL[44] for adults, aged 18 and above
    - Skindex 29[45] for adults, aged 18 and above.
    - EQ-5D-5L for aged 11 years plus adults.[46, 47]
    - CHU-9D[48] for children up to and including 17 years of age

7. Time burden of treatment: time per session for active light treatment and participant-reported treatment burden for TCS and light treatments during treatment phase.

Safety Outcomes

The safety endpoints are the number of adverse reactions during the treatment phase. Participants were asked to record any adverse events in their treatment diary and were also asked at 3, 6 and 9-month clinic visits about any adverse events they had experienced. Any adverse events deemed related to trial treatments (adverse reactions) were reported in the CRF. Erythema (redness) of grade 1 or 2 was not considered an adverse event, as this is an expected treatment response from use of NB-UVB. All serious adverse events (SAEs) were reported directly to the trial coordinating centre and assessed for seriousness, expectedness and causality by the Chief Investigator, or delegated medical monitor. SAEs were recorded and reported to the Medicines Health Regulatory Authority (MHRA) and Research Ethics Committee (REC) as part of the annual reports.

Cost-effectiveness analysis

The within-trial economic evaluation estimates the incremental cost effectiveness from an NHS perspective of:

I. NB-UVB light therapy (plus placebo ointment) compared to topical corticosteroid (plus dummy light)
II. Combination of NB-UVB light therapy and TCS compared to TCS (plus dummy light).

The economic analysis uses individual participant level data from the trial. The base case analysis undertakes a cost-effectiveness analysis from an NHS perspective for all participants. Secondary analyses consider the cost-utility of the comparators of interest for those with EQ-5D-5L data available (participants aged 11 years and over) and separately for those with CHU-9D data available (participants aged 5 to <18 years). Full details of the methods can be found in chapter 4, beginning on page 77.

Data collection

Trial data were entered into a web-based electronic Case Record Form (eCRF) (MACRO 4.2.1 version 3800, Elsevier, London, UK). Staff at research sites had access to data from their site only, with access controlled through person-specific login credentials. Access to the trial database and database maintenance was managed by NCTU.

In order to facilitate the data collection process, site staff members were provided with CRF workbooks that mirrored the data required for the electronic CRF. Investigators were asked to transcribe the data into the electronic CRF within 7 days of the data being collected where possible.

Participants used a Trial Handbook, which included a detailed treatment diary, adverse event record, the use of any healthcare resources and any prescribed medicines. Site staff reviewed these handbooks at 3, 6 and 9-month clinic visits and entered summary data into the electronic CRF.

The primary outcome was collected at the 9-month clinic visit. For those who did not attend this visit and who had not withdrawn from the trial, primary outcome data was obtained via telephone, post or text message where possible.

After the treatment period (9 months), follow-up continued for a further 12 months, with participant-completed questionnaires at 12, 15, 18 and 21 months. These questionnaires were sent either by post with the data entered and returned on paper, or via email using electronic

questionnaires designed by staff at NCTU. Reminders were sent (via email or post) if the questionnaire remained uncompleted after 2 weeks, and again after 3 weeks. Members of NCTU staff chased up outstanding questionnaires after 3 weeks via telephone.

2.8 Sample Size

The choice of minimum clinically important difference between the groups was informed by a survey of the clinical membership of the UK Dermatology Clinical Trials Network (UK DCTN). Standard care was assumed to be TCS monotherapy and so 'TCS plus dummy light therapy' is the comparator group for all treatment comparisons. There are two comparisons of primary interest:

I. NB-UVB light therapy (plus placebo ointment) compared to TCS (plus dummy light)
II. Combination of NB-UVB light therapy and TCS compared to TCS (plus dummy light).

Assuming that 15% of participants allocated to receive TCS (plus dummy light therapy) would achieve treatment success as defined by the primary outcome, 372 participants were required to detect an absolute difference of 20%, with 2.5% two-sided alpha and 90% power. Allowing for 15% non-collection of primary outcome data, an original sample size of 440 participants was set.

As there were limited data available to inform the sample size calculation for the trial, the Data Monitoring Committee conducted a planned sample size review in December 2016. This review resulted in a recommendation to increase the sample size to 516 participants in order to maintain 90% power to detect a risk difference of 20% between the TCS arm and the other two arms. The Trial Steering Committee and the funders approved this recommendation.

2.9 Statistical Methods

Analyses were pre-defined in a statistical analysis plan (SAP), which was signed off prior to database lock. Points of clarification to the SAP that were made after database lock are summarised (SeeAppendix 1)

Primary Outcome

The number and percentage of participants achieving 'treatment success' (defined as a response of either 'A lot less noticeable' or 'No longer noticeable' in response to the question "Compared to the

start of the study, how noticeable is the vitiligo now?") is reported for each treatment group at 9 months from randomisation.

The primary analysis was performed on the ITT analysis set, where multiple imputation was used to account for missing primary outcome data at 9 months. Prior to primary analysis, baseline characteristics were summarised further by treatment arms and the availability of primary outcome at 9 months, in order to check the missing at random assumption of multiple imputation.

Randomised groups were compared using a mixed effects model for binary outcome adjusted by recruitment centre, body region of the target patch, and age at randomisation (continuous). The primary effectiveness parameter comparing NB-UVB light with TCS alone, and NB-UVB light plus TCS with TCS alone, was the risk difference (risk ratio will also be included) in the percentage of participants achieving treatment success at 9 months along with 95% confidence interval and exact p-value. By default, risk differences are reported, because these estimates are more clinically intuitive for binary outcomes. However, where models estimating risk difference do not converge, odds ratios will be reported instead of risk differences.

Sensitivity analyses were conducted to (i) adjust for any variables with imbalance at baseline, (ii) repeat primary analysis based on participants whose primary outcome was available at 9 months and (iii) investigate the effects of treatment adherence.

Planned subgroup analyses were (i) children versus adults); (ii) body region of the target vitiligo patch; (iii) hypomelanotic patch (an indicator of disease activity): definitely or maybe versus no; (iv) ≥ 4 years duration of vitiligo versus <4 years. These analyses were conducted by inclusion of appropriate interaction terms in the regression model and were considered as exploratory. An additional post-hoc subgroup analysis explored the impact of skin type (types I to III versus types IV to VI).

Secondary Outcomes

I. VNS treatment success by blinded review of digital images at 9 months

Between-group comparisons were performed using mixed effect regression model for binary outcome, adjusting by recruitment centre, body region of target patch and age (continuous). The analysis was performed on a modified ITT set, where no imputation of missing data was required.

II. Participant-reported treatment success by body region (at 9 months):

VNS treatment success at 9 months for all assessed patches (up to 3) was analysed using a multi-level mixed effects model, accounting for potential correlation between treatment effects at different body regions within the same person. This analysis was conducted with multiple

imputation of missing treatment success data. Patient-reported treatment success by body region at 3 and 6 months is presented descriptively

III. Onset of treatment response (during treatment phase):

Summary data by all the 3 categories (stayed the same, improved, got worse) is presented by treatment group and by timeline (3, 6, 9 months). The cumulative percentage of participants who achieved a treatment response (stayed the same or improved) at target patch is presented. Analysis of treatment response at 9 months was analysed using a mixed effect regression model for binary outcome, adjusting by recruitment centre, body region of target patch and age (continuous).

Participant reported onset of treatment response is summarised as for investigator-assessed treatment response.

IV. Maintenance of treatment response (during follow up phase):

Maintenance of treatment response is presented separately for those who achieved and those who did not achieve treatment response at the end of the treatment phase. The cumulative percentage of participants with loss of maintenance of treatment response is presented by treatment arm. Data is reported for the target patch only.

V. Percentage repigmentation at 9 months (by blinded dermatologist and investigator):

Analysis of blinded dermatologist assessed percentage repigmentation at 9 months was analysed using a mixed effect regression model for binary outcome, adjusting by recruitment centre, body region of target patch and age (continuous). Where available, data from investigator assessments at 9 months were used for missing data based on blinded clinician assessment of digital images.

Treatment success based on investigator-assessed percentage repigmentation at 9 months is reported descriptively.

Assessments carried out by investigators at 3 and 6 and 9 months are presented descriptively.

VI. Quality of life at end of treatment (9 months) and end of follow-up (21 months).

Total scores for VITIQOL, Skindex 29, CHU-9D and EQ-5D questionnaires at 9 months and 21 months are summarised by treatment arm using appropriate summary statistics.

VII. Time burden of treatment:

For active light therapy, the average time per treatment session was estimated using data collected at 3, 6 and 9 months. Time burden of TCS application was assumed to be minimal. The percentage of those who reported difficulties with the interventions are summarised, along with a description of the difficulties experienced.

Chapter 3: Results: clinical findings

3.1 Recruitment and participant characteristics

Recruitment took place between May 2016 and September 2017, the database was closed for follow-up on 31st December 2018

A total of 1832 reply slips were received, of which 1093 received telephone screening and 549 clinic screening. Five hundred and seventeen participants (173 TCS only, 169 NB-UVB only and 175 combination) were randomised.

Primary outcome data at 9 months were available for 370 (72%) participants (See Figure 2).

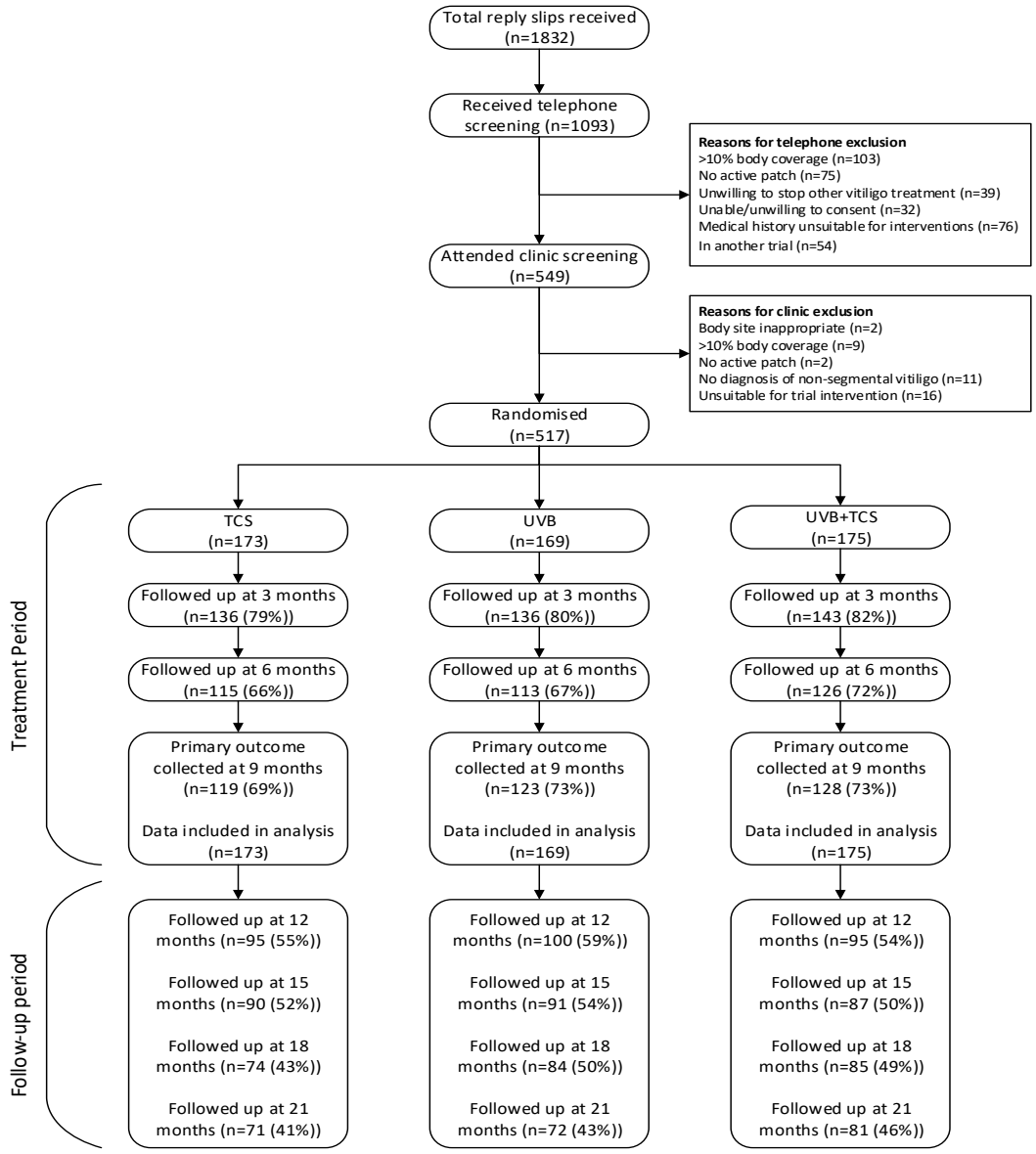

Figure 2 Consort Diagram

*Note reasons for non-collection of primary outcome at 9 months were: not assessed in clinic (n=4), withdrew consent (n=60), discontinued due to AE (n=3), lost to follow up (n=75) and other (n=5). These reasons were similarly distributed within each treatment arm. Of those withdrew consent, 11 stated that this was due to lack of treatment response and 33 due to time burden. Of those lost to follow up, 1 stated that this was due to lack of treatment response and 2 due to time burden.

Baseline characteristics and sources of recruitment are summarised in Table 4.

Participants were recruited from primary care (118/517, 23%), secondary care (213/517, 41%) and through self-referral from community advertising (186/517, 36%).

Baseline characteristics were well balanced across treatment groups. Almost a quarter of the participants were children (119 /517, 23%). There was an equal balance of genders (268 /517, 52% male) and the majority were white (330/517, 64%). Participants of all skin types were enrolled, the most common being skin type III (195/517, 38%). Baseline characteristics for participants providing primary outcome data and those not providing primary outcome data are summarised (

Table 5)

Table 4 Baseline characteristics

Characteristic	TCS	NB-UVB	Combination	Total
	(n = 173)	(n = 169)	(n = 175)	(n=517)
Age at randomisation (years)				
Mean(sd)	38.6[20.0]	36.9[18.9]	37.0[19.1]	37.5[19.3]
Age of adults at randomisation (years)				
Mean(sd)	46.7[15.2]	44.7[14.0]	44.8[14.2]	45.4[14.5]
N	133	130	135	398
Age of children at randomisation (years)				
Mean(sd)	11.7[3.7]	10.8[3.5]	10.6[3.3]	11.1[3.5]
N	40	39	40	119
Gender				
Male	75(43%)	88(52%)	105(60%)	268(52%)
Ethnicity				
White	112(65%)	114(67%)	104(59%)	330(64%)
Indian	13(8%)	13(8%)	10(6%)	36(7%)
Pakistani	12(7%)	15(9%)	27(15%)	54(10%)
Bangladeshi	4(2%)	4(2%)	4(2%)	12(2%)
Black	5(3%)	3(2%)	7(4%)	15(2%)
Chinese	2(1%)	1(1%)	1(1%)	4(1%)
Other Asian (Non-Chinese)	5(3%)	6(4%)	6(3%)	17(3%)
Mixed Race	9(5%)	6(4%)	6(3%)	21(4%)
Other	10(6%)	7(4%)	9(5%)	26(5%)
Missing	1(1%)	0	1(1%)	2(<0.5%)
Source of recruitment				
Primary care	35(20%)	36(21%)	47(27%)	118(23%)
Secondary care	74(43%)	67(40%)	72(41%)	213(41%)
Self-referral	64(37%)	66(39%)	56(32%)	186(36%)
Skin photo type				
Type I	2(1%)	2(1%)	5(3%)	9(2%)
Type II	31(18%)	32(19%)	29(17%)	92(18%)
Type III	70(40%)	66(39%)	59(34%)	195(38%)
Type IV	29(17%)	34(20%)	33(19%)	96(19%)
Type V	35(20%)	25(15%)	44(25%)	104(20%)
Type VI	6(3%)	10(6%)	5(3%)	21(4%)
Medical history				
Type I diabetes	5(3%)	3(2%)	4(2%)	12(2%)
Hyperthyroidism	4(2%)	2(1%)	6(3%)	12(2%)
Hypothyroidism	21(12%)	18(11%)	10(6%)	49(9%)
Addison's disease	2(1%)	0	3(2%)	5(1%)
Pernicious anaemia	5(3%)	3(2%)	6(3%)	14(3%)
Alopecia areata	3(2%)	7(4%)	3(2%)	14(3%)
Duration of vitiligo (years)				
Mean(sd)	11.5[12.0]	9.9[11.1]	11.3[10.5]	10.9[11.2]
Median (25^{th}, 75^{th} centile)	7[3,6]	5[3,11]	7[4,15]	7[3,15]
Min, max	1,60	1,60	1,45	1,60

Previous treatments used for vitiligo				
Light therapy	28(16%)	26(15%)	37(21%)	91(18%)
Corticosteroid cream/ointment	80(46%)	75(44%)	80(46%)	235(45%)
Calcineurin inhibitor	51(29%)	39(23%)	56(32%)	146(28%)
Cosmetic camouflage	45(26%)	44(26%)	40(23%)	129(25%)
Other	20(12%)	15(9%)	17(10%)	52(10%)

All data are N (%) unless otherwise indicated.

Table 5 Baseline characteristics by treatment group and availability of primary outcome at 9 months

Characteristic	TCS (n = 173)		NB-UVB (n = 169)		Combination (n = 175)	
	With primary outcome (n=119)	Without primary outcome (n=54)	With primary outcome (n=123)	Without primary outcome (n=46)	With primary outcome (n=128)	Without primary outcome (n=47)
Age at randomisation (years)						
Mean(sd)	39.9[21.2]	35.8[16.9]		35.2[14.9]	36.5[200.2]	38.3[15.7]
Median (25th Q, 75th Q)	43.6[17.5,58.7	32.4[22.4,49		34.4[25.5,43.6]	36.4[15.5,51.2]	39[26.7,46.5
Min, max	]	]	37.5[20.2]	10,68.7	5.4,78.1	]
Age of adults at randomisation (years)	6.1,84.5	6.6,65.1	39.5[15.8,52.8] 5.2,76.2			5.7,72.7
Mean(sd)				39.1[12.8]	46.6[14.3]	
Median (25th Q, 75th Q)	49.8[14.9]	40.6[14.2]		37.1[29.6,45.9]	46.5[35.9,55.9]	41.0[13.4]
Min, max	50.4[38.9,60.8	39.5[28.6,51	47.1[13.9]	18.1,68.7	19.2,78.1	40.3[30.8,47
Age of children at randomisation (years)	] 20,84.5	.8] 20.9,65.1	44.7[38.1,58.7] 18.4,76.2			.3] 18.4,72.7
Mean(sd)				13.8[2.0]	10.9[3.1]	
Median (25th Q, 75th Q)				14.6[12.3,15]	10.2[8.9,12.4]	
Min, max	11.7[3.7]	11.9[3.7]	10.2[3.4]	10,15.8	5.4,17.8	8.6[4.9]
	12[7.9,14.9]	10.3[10.2,14	9.7[7.3,13.2]			6.5[5.9,11.3]
	6.1,17.8	.1]	5.2,16			5.7,15.9
		6.6,17.6				
Gender						
Male	43(36%)	32(59%)	67(54%)	21(46%)	75(59%)	30(64%)
Female	76(64%)	22(41%)	56(46%)	25(54%)	53(41%)	17(36%)
Ethnicity						
White	74(62%)	38(70%)	85(69%)	29(63%)	77(60%)	27(57%)
Indian	11(9%)	2(4%)	8(7%)	5(11%)	9(7%)	1(2%)
Pakistani	9(8%)	3(6%)	10(8%)	5(11%)	21(16%)	6(13%)
Bangladeshi	3(3%)	1(2%)	3(2%)	1(2%)	3(2%)	1(2%)
Black	3(3%)	2(4%)	2(2%)	1(2%)	4(4%)	3(6%)
Chinese	1(1%)	1(2%)	1(1%)	0	1(1%)	0
Other Asian (Non-Chinese)	4(3%)	1(2%)	4(3%)	2(4%)	4(3%)	2(4%)
Mixed Race	7(6%)	2(4%)	4(3%)	2(4%)	3(2%)	3(6%)
Other	7(6%)	3(6%)	6(5%)	1(2%)	5(4%)	4(9%)
Missing	0	1(2%)	0	0	1(1%)	0
Source of recruitment						
Primary care	25(21%)	10(19%)	28(23%)	8(17%)	36(28%)	11(23%)
Secondary care	51(43%)	23(43%)	49(40%)	18(39%)	59(46%)	13(28%)
Self-referral	43(36%)	21(39%)	46(37%)	20(43%)	33(26%)	23(49%)
Medical history						
Type I diabetes	4(3%)	1(2%)	2(2%)	1(2%)	1(1%)	3(6%)
Hyperthyroidism	3(3%)	1(2%)	3(3%)	0	3(3%)	3(6%)
Hypothyroidism	15(13%)	6(11%)	15(12%)	3(7%)	7(5%)	3(6%)

Characteristic	TCS (n = 173)		NB-UVB (n = 169)		Combination (n = 175)	
	With primary outcome (n=119)	Without primary outcome (n=54)	With primary outcome (n=123)	Without primary outcome (n=46)	With primary outcome (n=128)	Without primary outcome (n=47)
Addison's disease	0	2(4%)	0	0	2(2%)	1(2%)
Pernicious anaemia	3(3%)	2(4%)	2(2%)	1(2%)	2(2%)	4(9%)
Alopecia areata	1(1%)	2(4%)	5(4%)	2(4%)	2(2%)	2(4%)
Skin photo type						
Type I	1(1%)	1(2%)	2(2%)	0	4(3%)	1(2%)
Type II	24(20%)	7(13%)	23(19%)	9(20%)	21(16%)	8(17%)
Type III	41(34%)	29(54%)	51(41%)	15(33%)	43(34%)	16(34%)
Type IV	23(19%)	6(11%)	21(17%)	13(28%)	22(17%)	11(23%)
Type V	28(24%)	7(13%)	20(16%)	5(11%)	37(29%)	7(15%)
Type VI	2(2%)	4(7%)	6(5%)	4(9%)	1(1%)	4(9%)
Duration of vitiligo (years)						
Mean(sd)	11.8[12.9]	10.7[9.9]	9.7[11.2]	10.6[10.9]	10.8[10.3]	12.8[10.9]
Median (25^{th} Q, 75^{th} Q)	7[3,15.5]	7[3,20]	5[2,10]	7.5[4,12.5]	7[3,15]	8[5,20]
Min, max	1,60	1,41	1,60	1,57	1,45	1,42
Previous treatments used for vitiligo						
Light therapy	18(15%)	10(19%)	18(15%)	8(17%)	29(23%)	8(17%)
Corticosteroid cream/ointment	55(46%)	25(46%)	54(44%)	21(46%)	62(48%)	18(38%)
Calcineruin inhibitor	41(34%)	10(19%)	27(22%)	12(26%)	46(36%)	10(21%)
Costimetic camouflage	34(29%)	11(20%)	34(28%)	10(22%)	32(25%)	8(17%)
Other	17(14%)	3(6%)	10(8%)	5(11%)	10(8%)	7(15%)

All data are N (%) unless otherwise indicated.

The active target patches were located on the head and neck for 31% (161/517) participants, hands and feet for 32% (164/517), and the rest of the body for 37% (192/517). Not all participants chose to treat and assess three patches of vitiligo: 31% (162/517) chose one patch; 43% (224/517) chose two patches and 25% (131/517) chose three patches for assessment. Over half of the participants chose to treat patches in addition to the three being formally assessed in the trial, with 29% (148/517) of participants electing to treat six of more patches (See Table 6).

Table 6 Description of vitiligo patches at baseline

Target patch location	**TCS**	**NB-UVB**	**Combination**	**Total**
	(n = 173)	**(n = 169)**	**(n = 175)**	**(n=517)**
Head and neck	53(31%)	52(31%)	56(32%)	161(31%)
Hands and feet	56(32%)	53(31%)	55(31%)	164(32%)
Rest of the body	64(37%)	64(38%)	64(37%)	192(37%)
Total number of assessed patches included in study				
1	50(29%)	50(30%)	62(35%)	162(31%)
2	74(43%)	77(46%)	73(42%)	224(43%)
3	49(28%)	42(25%)	40(23%)	131(25%)
Total number of patches the participant would like to treat				
1	13(8%)	12(7%)	14(8%)	39(8%)
2 or 3	61(35%)	62(37%)	67(38%)	190(37%)
4 or 5	52(30%)	49(29%)	39(22%)	140(27%)
6 or more	47(27%)	46(27%)	35(31%)	148(29%)
Activity of target patch				
Hypomelanotic with poorly defined border				
Definitely	52(30%)	46(27%)	52(30%)	150(29%)
Maybe	14(8%)	20(12%)	18(10%)	52(10%)
No	107(62%)	103(61%)	105(60%)	315(61%)
Amelanotic with sharply defined border				
Definitely	97(56%)	101(60%)	99(57%)	297(57%)
Maybe	10(12%)	19(11%)	19(11%)	58(11%)
No	56(32%)	49(29%)	56(32%)	161(31%)

All data are N (%) unless otherwise indicated.

3.2 Adherence to trial treatment and treatment burden

Adherence is reported in Table 7. The median percentage of NB-UVB treatment days, as a percentage of expected days of treatment, was 81%, 77% and 74% for the three groups respectively, and for ointment 79%, 83% and 77%. Just under half of the participants used the treatment for ≥75% of the expected number of occasions, which was used as an indicator of good adherence in the sensitivity analyses of the primary outcome accounting for treatment adherence. Just over a quarter

of participants in all group discontinued one or more of the treatments before the end of the 9-month treatment phase.

For participants using active light devices the median time taken to administer the treatment was approximately 20 minutes, including time for set-up, administering the light, and documenting timings and side-effects in the treatment diary. In addition to written and online video training, participants required just over an hour (mean 70 minutes) of face to face training with a trained healthcare professional (usually a nurse) prior to using the treatment at home.

Difficulties in using the treatments are summarised (Table 7). Burden of treatment was identified as an issue by 42/142 (30%) in the TCS group, 38/140 (27%) in the NB-UVB group and 36/149 (24%) in the combination group, although interpretation is difficult as all three groups used both treatments throughout (either active or dummy/placebo). Not surprisingly, NB-UVB treatment was more burdensome than treatment with TCS. Burden of treatment and side-effects were the most commonly cited difficulties for both groups and were common reasons for discontinuation of treatment, along with lack of treatment response.

Table 7 Treatment adherence, burden and discontinuation

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)
Use of light treatment: reported number of treatment sessions as percentage of expected			
Mean[SD]	68%[31%]	68%[28%]	67%[27%]
Median[IQR]	81%[43%,95%]	77%[51%,90%]	74%[48%,89%]
Distribution of light adherence			
<25%	19(11%)	16(9%)	14(8%)
25-49%	21(12%)	18(11%)	26(15%)
50-74%	23(13%)	31(18%)	35(20%)
>=75%	82(47%)	72(43%)	74(42%)
Data not available	28(16%)	32(19%)	26(15%)
Use of ointment treatment: reported number of treatment sessions as percentage of expected			
Mean[SD]	68%[29%]	73%[27%]	68%[28%]
Median[IQR]	79%[47%,93%]	83%[57%,95%]	77%[45%,92%]
Distribution of ointment adherence			
<25%	16(9%)	12(7%)	13(7%)
25-49%	22(13%)	16(9%)	28(16%)
50-74%	30(17%)	27(16%)	30(17%)
>=75%	74(43%)	81(48%)	77(44%)
Data not available	31(18%)	33(20%)	27(15%)
Participant reported average duration (median[IQR] minutes, N) per light treatment session at			
3 months		20[10,30], N=135	15[10,30], N=142
6 months		22.5[12,42.5], N=120	20[15,35], N=124
9 months		20[13,40], N=101	20[12,30], N=111

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)
Burden of treatment:			
NB-UVB burden reported	36/142(25%)	35/140(25%)	32/149(21%)
TCS burden reported	18/142(13%)	14/140(10%)	14/149(9%)
Any burden reported (from either treatment)	42/142(30%)	38/140(27%)	36/149(24%)
Participants experienced difficulty using active light during the 9-month treatment period		76/140 (54%)	81/149(54%)
Difficulties experienced *			
Uncertainty of using light		7	18
Treatment burden		35	32
Side effect		37	43
Other		9	4
Participants experienced difficulty using active TCS treatment during the 9-month treatment period	35/142(25%)		31/149(21%)
Difficulties experienced *			
Uncertainty of using TCS	5		6
Treatment burden	18		14
Side effect	12		15
Other	4		0
Participants discontinued NB-UVB	50(29%)	47(28%)	43(25%)
Number discontinued within first 3 months	17(10%)	22(13%)	10(6%)
Reasons for NB-UVB discontinuation*			
All assessment patches repigmented	1	1	3
Time burden associated with treatment	23	20	17
Side effects	4	9	4
Lack of treatment response	9	3	7
Other	13	14	12

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)
Participants discontinued TCS	48(28%)	41(24%)	43(25%)
Number discontinued within first 3 months	17(10%)	19(11%)	10(6%)
Reasons for TCS discontinuation*			
All assessment patches repigmented	1	1	3
Time burden associated with treatment	20	17	15
Side effects	3	1	5
Lack of treatment response	9	5	7
Other	15	17	13

*Not mutually exclusive as participant can have multiple difficulties

3.3 Blinding

At the 9-month clinic visit, investigators reported that they thought they had become unblinded for 21% (31/145), 28% (43/153) and 27% (41/153) of participants in the TCS, NB-UVB and combination groups respectively. Participants were more likely to report that they thought they had become unblinded; 39% (45/116), 55% (66/120) and 44% (55/125) for the TCS, NB-UVB and combination groups respectively. Of the 115 investigators who thought they had been unblinded, 78% (90/115) thought it was due to either presence or absence of erythema.

Of those who indicated possible unblinding and were having NB-UVB, 83% (96/115) of investigators and 80% (132/166) of participants were correct. Of those who indicated possible unblinding and were having TCS, 32% (37/115) of investigators and 39% (64/166) of participants were correct. (Table 8).

Table 8 Unblinding of investigators and participants at 9 months

	TCS	NB-UVB	Combination
Number of investigators	145	153	153
Number unblinded	31(21%)	43(28%)	41(27%)
Of those who indicated unblinding:			
Investigator guess of light treatment received			
Correct	27(87%)	35(81%)	34(83%)
incorrect	4(13%)	8(19%)	7(17%)
Investigator guess of TCS treatment received			
Correct	21(68%)	4(9%)	12(29%)
Incorrect	10(32%)	39(91%)	29(71%)
Number of participants	116	120	125
Number unblinded	45(39%)	66(55%)	55(44%)
Of those who indicated unblinding:			
Participant guess of light treatment received			
Correct	25(56%)	59(89%)	48(87%)
incorrect	20(44%)	7(11%)	7(13%)
Participant guess of TCS treatment received			
Correct	23(51%)	23(35%)	18(33%)
incorrect	22(49%)	43(65%)	37(67%)

3.4 Primary Outcome

The percentage of participants who reported a treatment success (VNS) at 9 months was 17% (20/119) for the TCS only group, 22% (27/123) for NB-UVB only group and 27% (34/128) for the combination group. For participants where primary outcome was obtained, 96% (355/370) were obtained face-to-face at the 9-month clinic visit, 2% (9/370) via post, 1% (3/370) via telephone and 1% (3/370) via text message. Primary analysis was performed using multiple imputation. Adjusted

risk difference was 5.2% (95% CI -4.4% to 14.9%; p= 0.29) for NB-UVB only compared with TCS only, and 10.9% (95% CI 1.1% to 20.9%; p= 0.03) for combination compared with TCS only (Table 9). The number needed to treat (NNT) for NB-NB-UVB compared to TCS was 19 and for combination compared to TCS was 10.

An additional 29.5% (109/370) participants achieved a 'partial treatment response' (slightly less noticeable on the VNS): 24% (28/119) in the TCS group, 29% (36/123) in the NB-UVB group and 35% (45/128) in the combination group (Table 9).

The percentage of participants with a treatment success at 3 and 6 months is shown in Table 9.

Images demonstrating examples of good and poor treatment responses are shown in Figure 3.

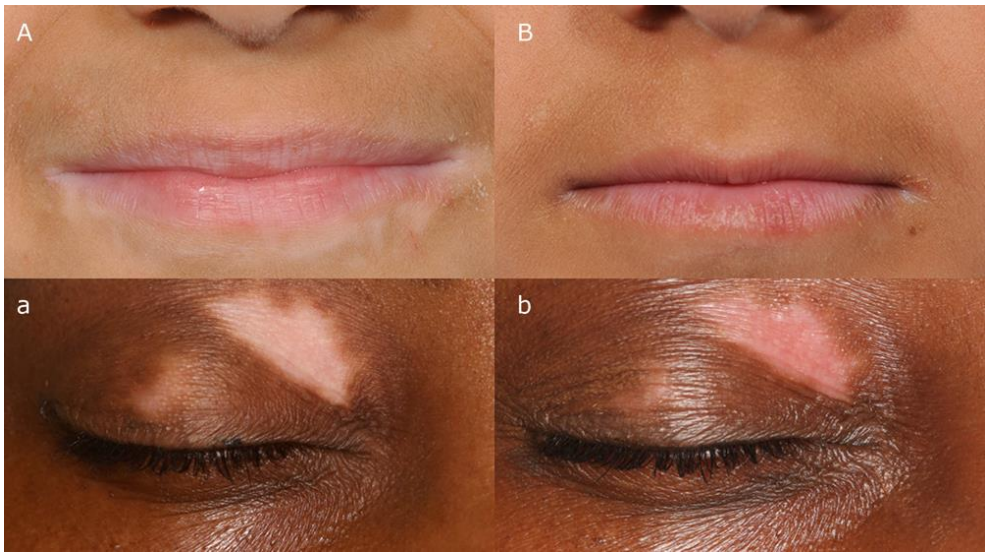

Figure 3 Figure showing target lesions before (A, a) and after (B, b) treatment.

Table 9 Primary outcome analysis – participant reported treatment success (VNS), intention-to-treat (ITT)

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)	Between-group comparisons (ITT)			
Patient response to VNS scale at 3 months							
More noticeable	16(12%)	26(19%)	15(10%)				
As noticeable	70(52%)	57(42%)	62(43%)				
Slightly less noticeable	34(25%)	34(25%)	47(33%)				
A lot less noticeable	13(10%)	19(14%)	17(12%)				
No longer noticeable	2(1%)	0	2(1%)				
Patient response to VNS scale at 6 months							
More noticeable	11(10%)	23(20%)	10(8%)				
As noticeable	51(44%)	37(33%)	36(29%)				
Slightly less noticeable	37(32%)	33(29%)	45(36%)				
A lot less noticeable	14(12%)	18(16%)	28(22%)				
No longer noticeable	2(2%)	2(2%)	7(6%)				
Participants with primary outcome data at 9 months	**119(69%)**	**123(73%)**	**128(73%)**	**NB-UVB vs TCS**		**Combination vs TCS**	
				Adjusted^ risk difference (95% CI)	Adjusted risk ratio (95% CI)	Adjusted risk difference (95% CI)	Adjusted risk ratio (95% CI)
Patient response to VNS scale at 9 months							
More noticeable	18(15%)	27(22%)	17(13%)				
As noticeable	53(45%)	33(27%)	32(25%)				
Slightly less noticeable	28(24%)	36(29%)	45(35%)	5.2%	1.44(0.77,2.70)	10.9%	1.93(1.02,3.68)
A lot less noticeable	15(13%)	25(20%)	27(21%)	(-4.4%,14.9%)		(1.1%,20.9%)	
No longer noticeable	5(4%)	2(2%)	7(5%)				
Patient reported treatment success* using VNS scale at 9 months	**20(17%)**	**27(22%)**	**34(27%)**				

All data are N (%) unless otherwise indicated.

*Treatment success will be defined as answer to either A lot less noticeable or No longer noticeable.

^Adjusted by centre, body region of target patch and age of participant with vitiligo.

Based on multiple imputation.

Sensitivity analyses were performed: 1) with further adjustment of baseline data; 2) only on participant with primary outcome data at 9 months; 3) accounting for adherence to trial treatment. Results from sensitivity analyses were consistent with the primary analysis. Participants who adhered to treatment interventions by ≥75% of expected treatments were more likely to achieve a treatment success. Adjusted odds ratio 1.91 (95% CI 0.87, 4.19) for NB-UVB compared with TCS, and 2.67 (95% CI 1.19, 5.99) for combination compared with TCS (Figure 4).

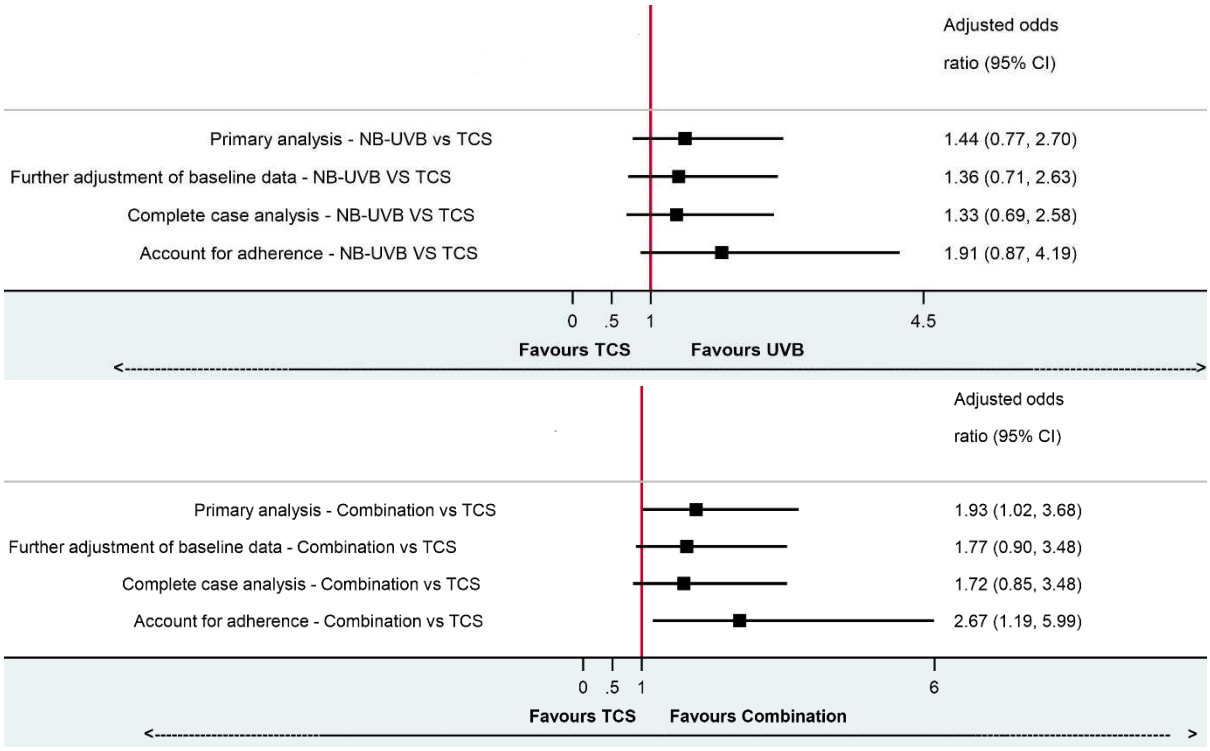

Figure 4 Sensitivity analyses of primary outcome

Further adjustment of baseline was for gender.
Complete case analysis was based on available data without imputation.
CACE analyses were performed to account for the impact of treatment adherence.

Subgroup analyses of the primary outcome were performed according to: 1) body region of the target patch (head & neck, hands & feet, rest of the body); 2) age (adults, children); 3) hypomelanotic patch with poorly defined borders (definitely/maybe, no); 4) duration of vitiligo (<4 years, ≥ 4 years); and 5) post hoc analysis by skin type (I to III, skin type IV to VI).

No differences were found between the groups for any of the planned and post-hoc sub-groups, with the exception of body region of the target patch, where analyses based on patches on the rest of the body appeared to favour combination treatment compared to TCS (Table 10).

Table 10 Summary of subgroup analysis for the primary outcome (target patch only)

	VNS treatment success rate			NB-UVB Vs TCS Odds ratio^ (95% CI)	Combination Vs TCS Odds ratio (95% CI)
	TCS	NB-UVB	Combination		
By body region of target patch					
Adjusted* Odds Ratio (95% CI)					
Head and neck (N=161)	10(29%)	15(42%)	11(26%)	1.78(0.70,4.52)	1.15(0.43,3.09)
Hands and feet (N=164)	2(5%)	4(12%)	4(13%)	1.93 (0.35,10.78)	2.56(0.45,14.77)
Rest of body (N=192)	8(17%)	8(15%)	19(36%)	1.01(0.38,2.68)	2.88(1.06,7.80)
By age					
Adjusted Odds Ratio (95% CI)					
Adults (N=398)	13(15%)	20(22%)	22(24%)	1.64(0.76,3.55)	2.03(0.93,4.43)
Children (N=119)	7(23%)	7(22%)	12(33%)	1.03(0.26,4.04)	1.80(0.60,5.37)
By hypomelanotic and poorly defined border					
Adjusted Odds Ratio (95% CI)					
Definitely or Maybe (N=202)	10(22%)	11(20%)	16(30%)	1.05(0.41,2.67)	1.72(0.64,4.66)
No (N=315)	10(14%)	16(23%)	18(24%)	1.78(0.83,3.82)	2.08(0.92,4.68)
By duration of vitiligo					
Adjusted Odds Ratio (95% CI)					
≥ 4 years (N=348)	11(14%)	14(21%)	18(20%)	1.68(0.73,3.82)	1.72(0.76,3.87)
< 4 years (N=150)	8(22%)	10(20%)	16(47%)	0.99(0.29,3.49)	3.28(0.91,11.92)
By skin type					
Adjusted Odds Ratio (95% CI)					
Skin type I to III (N=296)	10(15%)	14(18%)	14(21%)	1.18(0.54, 2.59)	1.38(0.64, 2.96)
Skin type IV to VI (N=221)	10(19%)	13(28%)	20(33%)	1.64(0.57, 4.78)	2.56(0.63, 10.37)

All data are N (%) unless otherwise indicated.
*Adjusted by centre, body region of target patch and age of participant with vitiligo. Analysis with multiple imputation
^Due to model convergence only odds ratios were possible to be obtained for between group comparisons.

3.5 Secondary Outcomes

VNS treatment success from blinded PPI reviewers

Treatment success from blinded image assessment by patient reviewers were broadly consistent with the primary analysis but were more likely to suggest benefit from NB-UVB, with evidence of significant differences in treatment success for both the NB-UVB and the combination groups, compared with TCS (Table 11).

Table 11 Treatment success by blinded PPI assessors (VNS using digital images at baseline and 9 months)

	TCS	NB-UVB	Combination	Between-group comparisons			
TREATMENT PHASE				**NB-UVB vs TCS**		**Combination vs TCS**	
				Adjusted^ risk difference (95% CI)	Adjusted risk ratio (95% CI)	Adjusted risk difference (95% CI)	Adjusted risk ratio (95% CI)
Treatment success by blinded PPI assessors at 9 months (target patch)	11%(12/112)	20%(22/108)	28%(32/116)	9.7% (1.2%, 18.2%)	2.22(1.14, 4.31)	16.3% (7.0%, 25.6%)	3.52(1.80, 6.89)

All data are N (%) unless otherwise indicated.

^Analyses adjusted by centre, body region of target patch and age of participant with vitiligo

Participant reported VNS treatment success by region of the body (including all assessed patches)

Patches on the hands and feet were less likely to respond to treatment than other parts of the body, regardless of the treatments being used. However, the between group comparisons given in Table 12 indicate that there was no evidence of a differential treatment effect according to the location of assessed patches. (Table 12 and Figure 5). Participant-reported VNS at 3 and 6 months by body region is summarised (See Appendix 2).

Figure 5 Treatment success at all assessed patches at 9 months

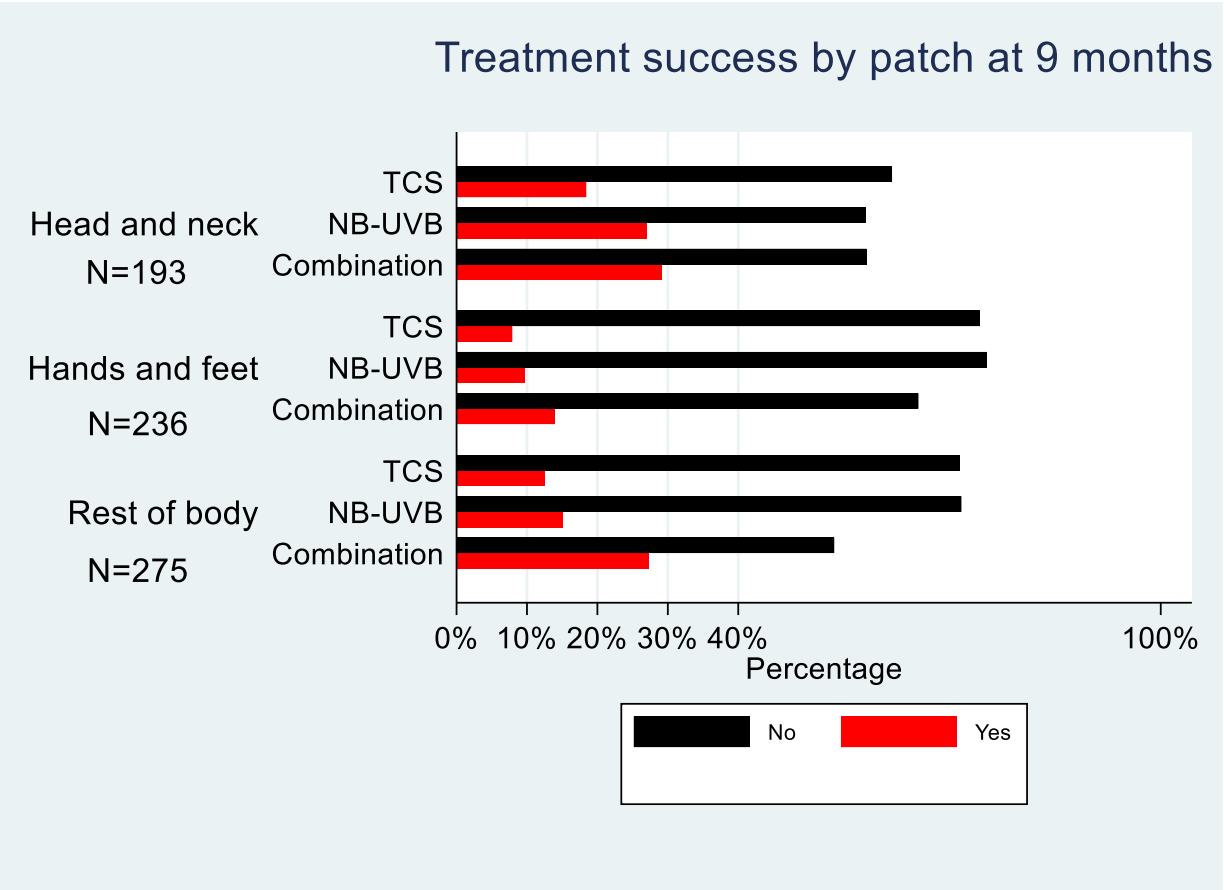

Table 12 Participant reported treatment success (VNS) by body region (including all assessed patches)

	TCS	NB-UVB	Combination	Between-group comparisons			
TREATMENT PHASE				**NB-UVB vs TCS**		**Combination vs TCS**	
Participant reported treatment success at 9 months by body regions (maximum 3 patches per person)				Adjusted* Odds Ratio^ for interactions (95% CI)		Adjusted Odds Ratio for interactions (95% CI)	
Head and neck	23%(14/61)	32%(20/63)	33%(23/69)	Hands and Feet vs Head and Neck	0.89(0.22,3.54)	Hands and Feet vs Head and Neck	1.30(0.31,5.52)
Hands and feet	10%(8/83)	11%(7/79)	18%(13/74)				
Rest of body	15%(14/94)	17%(16/92)	34%(30/89)	Rest of body vs Head and Neck	1.06(0.30,3.74)	Rest of body vs Head and Neck	2.42(0.67,8.76)

All data are N (%) unless otherwise indicated.

*Analyses adjusted by centre, body region of target patch and age of participant with vitiligo

^Due to model convergence only odds ratios were possible to be obtained for between group comparisons.

Overall 94% of participants had achieved onset of treatment response by 3-months for all groups (defined as the active target patch having improved or stayed the same (not worsened) as assessed by investigators) (Figure 6). TCS (40% improved 57% stayed the same); NB-UVB (61% improved, 35% stayed the same) and combination (60% improved, 38% stayed the same).

Participant reported onset of treatment response is summarised (Appendix 3).

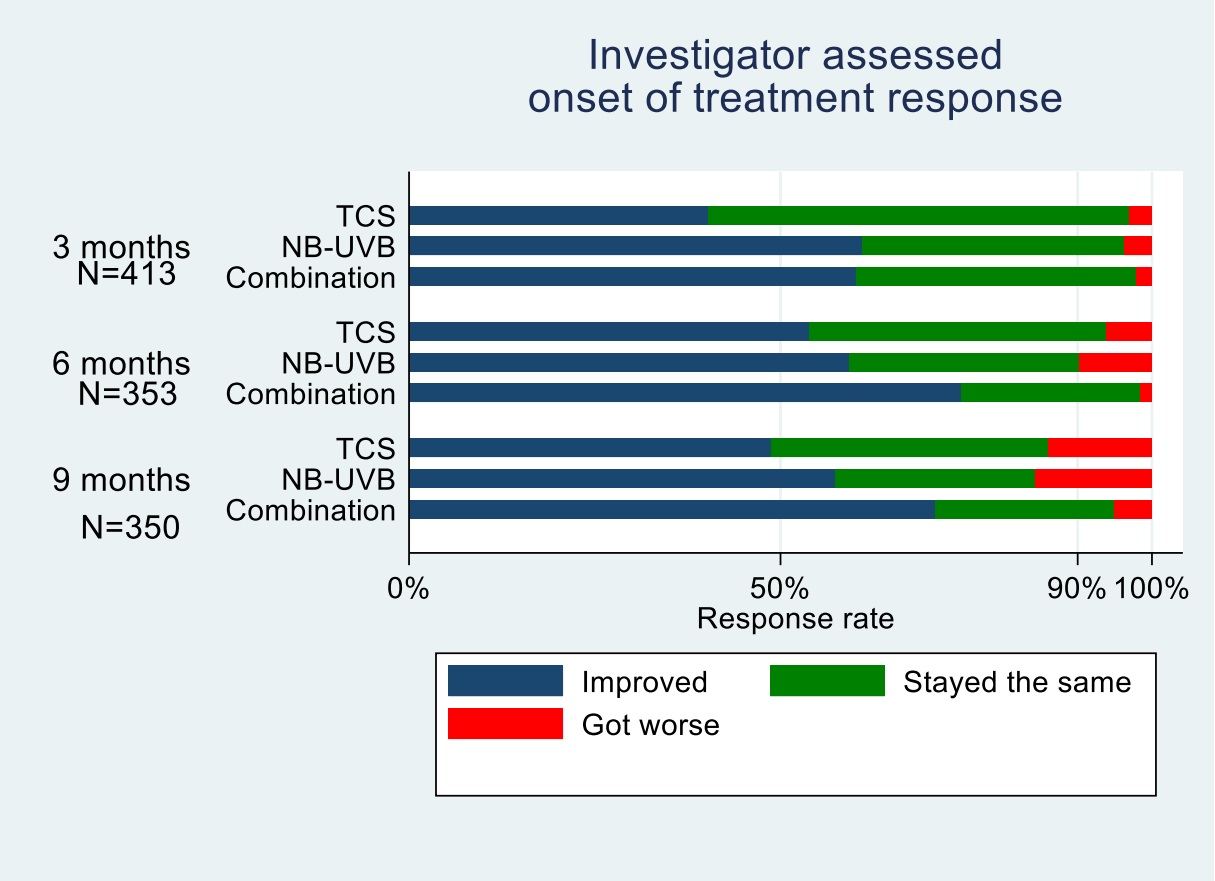

Figure 6 Investigator assessed onset of treatment response

Treatment success - percentage repigmentation

Percentage repigmentation was assessed by a dermatologist using digital images taken at baseline and 9 months. Results were supportive of the primary outcome, although the rates of treatment success were lower: 3% (4/115) for the TCS group, 8% (9/116) for the NB-UVB group and 15% (18/120) for the combination group. Adjusted odds ratio 2.22 (95% CI 0.66, 7.51) for NB-UVB compared with TCS, and 4.62 (95% CI 1.50, 14.24) for combination compared with TCS (Table 9 Percentage repigmentation assessed by blinded dermatologist and investigators). Review by blinded

investigators during clinic visits were also supportive of the primary outcome (Table 13). Full details of repigmentation rates at all time points are summarised (Appendix 4).

Table 13 Percentage repigmentation assessed by blinded dermatologist and investigators

	TCS	**NB-UVB**	**Combination**	**Between-group comparisons**	
TREATMENT PHASE				**NB-UVB vs TCS**	**Combination vs TCS**
% repigmentation - treatment success at 9 months assessed by blinded dermatologist (using digital images of target patch)	3%(4/115)	8%(9/116)	15%(18/120)	Adjusted* Odds Ratio^ (95% CI) 2.22(0.66, 7.51)	Adjusted Odds Ratio (95% CI) 4.62(1.50, 14.24)
% repigmentation - treatment success assessed by investigators (target patch) at					
3 months	3%(4/134)	4%(6/136)	4%(6/143)		
6 months	7%(8/115)	5%(6/113)	11%(14/125)		
9 months	9%(10/134)	10%(11/136)	18%(21/143)		

All data are N (%) unless otherwise indicated.

*Analyses adjusted by centre, body region of target patch and age of participant with vitiligo

^Due to model convergence only odds ratios were possible to be obtained for between group comparisons.

Long-term follow-up (post-intervention)

Long term follow-up rates at 12,15,18 and 21 months were 56%, 52%, 47% and 43%, and so results are presented descriptively.

By 21 months (12 months after stopping treatment), just over 40% (149/338) of participants reported that repigmentation had been lost (Table 14). These percentages were similar for those who achieved 'treatment success' at 9 months (Table 15).

Table 14 Loss of treatment response at target patch assessed by participant at 12, 15, 18 and 21 months

	TCS	NB-UVB	Combination
LONG-TERM FOLLOW-UP PHASE			
Loss of treatment response at target patch assessed by participant at			
12 months	19%(18/95)	23%(23/100)	19%(18/95)
15 months	30%(31/105)	35%(39/111)	30%(32/107)
18 months	37%(39/107)	40%946/116)	37%(41/112)
21 months	46%(50/108)	43%(50/116)	43%(49/114)

All data are N (%) unless otherwise indicated.

Table 15 Loss of treatment response at target patch assessed by participant at 12, 15, 18 and 21 months (only for those who achieved treatment success by 9 months)

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)
LONG-TERM FOLLOW-UP PHASE			
Loss of treatment response at target patch assessed by participant at			
12 months	6%(1/17)	13%(3/23)	28%(7/25)
15 months	28%(5/18)	36%(9/25)	36%(10/28)
18 months	33%(6/33)	38%(10/26)	38%(11/29)
21 months	33%(6/18)	38%(10/26)	47%(14/30)

All data are N (%) unless otherwise indicated.

Participant reported VNS throughout the trial (treatment and follow-up)

VNS scores throughout the study treatment period (0 to 9 months) and follow-up period (12 to 21 months) are shown (Figure 7). The number included at each timepoint varies according to follow-up completion rates, but shows treatment success to be achieved by 6 months in the combination group and maintained for approximately 3 months, before loss of gained pigmentation in the longer term.

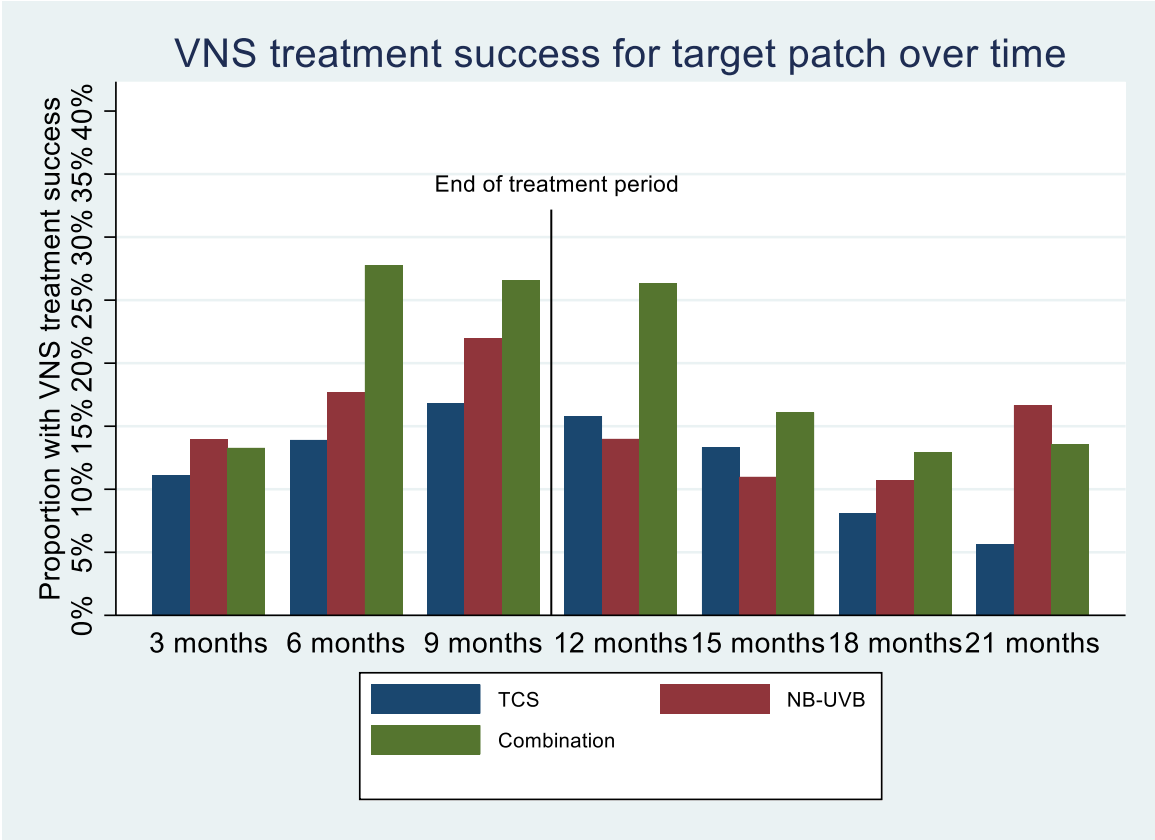

Figure 7 Percentage of participants reporting treatment success for target patch during the trial

Quality of life

There was no difference between the groups in any of the generic or vitiligo-specific quality of life instruments at any timepoint (Table 16)

Table 16 Summary of quality of life scores

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)	Between-group comparisons	
				NB-UVB vs TCS	Combination vs TCS
At baseline					
VitiQOL score (adults)					
Mean(sd)	34.7[21.8]	33.3[23.8]	35.6[23.3]		
N	133	129	135		
Skindex 29 score (adults)					
Mean(sd)	22.8[15.7]	21.4[18.6]	23.8[18.7]		
N	132	130	133		
EQ-5D utility score (all)					
Mean(sd)	0.9[0.1]	0.9[0.2]	0.9[0.2]		
N	151	140	147		
CHU-9D utility score (children)					
Mean(sd)	1[0.1]	0.9[0.1]	0.9[0.1]		
N	40	35	39		
At 9 months					
VitiQOL score (adults)				Adjusted difference in means (95% CI)	Adjusted difference in means (95% CI)
Mean(sd)	32.7[21.2]	27.9[22.0]	31.7[21.5]	-5.5(-11.8, 0.8)	-2.0(-8.3, 4.4)
N	85	85	85		
Skindex 29 score (adults)				Adjusted difference in means (95% CI)	Adjusted difference in means (95% CI)
Mean(sd)	19.2[14.9]	17.5[16.6]	20.3[15.6]	-2.2(-6.8, 2.4)	0.3(-4.3, 4.9)
N	82	83	84		
EQ-5D utility score (all)			0.9[0.1]98	Adjusted difference in means (95% CI)	Adjusted difference in means (95% CI)
Mean(sd)	0.9[0.2]	0.9[0.1]		0.045(0.003,0.087)	0.031(-0.010,0.073)
N	97	89			
CHU-9D utility score (children)				Adjusted difference in means (95% CI)	Adjusted difference in means (95% CI)
Mean(sd)	1[0.1]	1[0]	0.9[0.1]	0(-0.028,0.027)	-0.023(-0.048,0.002)
N	31	28	35		
At 21 months					
VitiQOL score (adults)					
Mean(sd)	36.1[21.1]	31.1[22.8]	38.4[23.6]		
N	56	57	63		
Skindex 29 score (adults)					
Mean(sd)	22.5[16.5]	19.1[16.6]	25.9[17.5]		
N	57	52	60		

Lower score means better outcome for VitiQOL, Skindex. Higher score means better outcome for EQ-5D and CHU-9D

Adverse and serious adverse events

Safety

A total of 124 (25%) participants reported 206 related-adverse events, 33 events from 24 participants (14%) in the TCS group, 69 events from 48 participants (28%) in the NB-UVB group and 104 from 52 participants (30%) in the combination group. A full listing of related-adverse events are provided in Appendix 5. There were five serious adverse events reported from five participants, but none were related to trial interventions (See Table 17)

Details of grades 3 or 4 erythema and skin thinning are shown (See Table 17). In general, fewer adverse events were reported in children than adults.

There were five reported Serious Adverse Events, but none was related to trial treatments. These were asthma, fracture, pancreatitis, pneumonia and syncope.

Table 17 Adverse events

	TCS (n = 173)	NB-UVB (n = 169)	Combination (n = 175)
Total number of participants reported any related AEs	24(14%)	48(28%)	52(30%)
Total number of related AEs	33	69	104
AEs by severity			
Mild	30	32	58
Moderate	3	24	40
Severe	0	13	6
AEs by outcome			
Recovered	20	53	92
Resolved with sequelae	3	6	3
Ongoing	7	5	6
Unknown	3	5	3
Number of erythema events in adults	2(2)	22(20)	37(26)
Grade 3 erythema	0	8	33
Grade 4 erythema	2	14	4
Number of erythema events in children	1(1)	7(6)	8(7)
Grade 3 erythema	1	6	8
Grade 4 erythema	0	1	0
Erythema events by outcome	3	29	45

Recovered	3	25	44
Resolved with sequelae	0	1	0
Ongoing	0	0	1
Unknown	0	3	0
Number of skin thinning* event in adults	5(5)	2(2)	5(5)
Number of skin thinning events in children	1(1)	0	0
Skin thinning events by outcome	6	2	5
Recovered	3	1	2
Resolved with sequelae	0	1	2
Ongoing	2	0	1
Unknown	1	0	0

*Skin thinning was defined as any events classified as skin atrophy, skin striae, telangiectasia or spider vein.

Chapter 4: Health Economic Evaluation

4.1 Introduction

A systematic review in 2018 showed that the economic evidence base for vitiligo treatment and care is virtually non-existent[49]. One of the two studies identified in this review estimated the annual direct cost of treating vitiligo in the USA to be $15,000,000 for the price year 2004[50]. The other study demonstrated that 32.5% of people with vitiligo would be willing to make a one-off payment of €5000 for a cure (2006 price year)[51], allowing an estimate of the maximum potential for benefit should a cure be found. These papers indicate the cost both to the person affected and the health care system but do not provide evidence to inform resource allocation decisions. No papers were identified that undertook full economic evaluations of vitiligo treatments either alongside clinical trials or as economic modelling. Mcmanus et al.[49], identified a need for full economic evaluations of currently prescribed vitiligo treatments. This chapter reports what we believe to be the first full economic evaluation of vitiligo treatment, both of a current standard treatment (TCS) and new treatment (home based NB-UVB light therapy) alone and in combination with TCS. In this chapter the methods, results and discussion pertaining to the economic evaluation undertaken alongside the trial are reported.

4.2 Methods

The primary objective of the health economic evaluation was to estimate the within-trial cost-effectiveness of i) active hand-held NB-UVB light compared to TCS only (standard care) and ii) active hand-held NB-UVB plus TCS compared to TCS only (standard care) in terms of cost per treatment success at the end of the treatment period (9 months) in the treatment of vitiligo, using individual level data collected within the trial. These were deemed the appropriate economic questions as each compares to current standard care.

The secondary objective was to undertake two separate cost utility analyses at the end of the trial intervention period (9 months) for those with (i) EQ-5D-5L utility values available (participants aged 11 and over years) and (ii) CHU-9D utility values available (participants aged 5 to <18 years). Including the EQ-5D-5L values of those aged 11-17 in (i) deviates slightly from what was proposed in the protocol in recognition that lower than expected response rates to the utility instruments, particularly at follow-up, means it makes more sense to use all the data available regardless of age.

The evaluation was undertaken in line with published guidelines for the economic evaluation of health care interventions as appropriate[52-56].

The trial was conducted in the UK, which has a national health service (the NHS), providing publicly funded healthcare that is largely free of charge at the point of use. Therefore the analysis was primarily undertaken from an NHS perspective, in keeping with the NICE reference case.[56] Out of pocket costs incurred by participants and where applicable their parents/guardians arepresented separately reflecting a personal perspective.

The primary economic analysis compares the costs and outcomes over the 9-month intervention period from randomisation and therefore costs and benefits are not discounted.

4.3 Resources use and costs

Identification of resources

In keeping with the chosen perspective, the base case captured the intervention costs (including any side-effect costs) to the NHS and the participant's wider use of the NHS (including health care visits and prescriptions) as a result of vitiligo. Participants' personal out of pocket expenses incurred as a result of their vitiligo were also captured in a separate analysis taking a broader perspective. The time spent by patients administering the interventions is presented descriptively elsewhere in this report, but participant time burden administering treatment was not costed.

Measurement of resource use data

Resource use for the intervention phase was collected at 3, 6 and 9 months, using information recorded by participants in daily diaries and in case report forms collected at follow-up visits. In the follow-up period, resource use was collected via online participant questionnaires at 12, 15, 18 and 21 months (or via paper copies if preferred).

Valuation of resource use data

The cost of the intervention was estimated at the individual level as follows.

NB-UVB Device:

In costing the intervention, the cost of the hand-held device was estimated using the manufacturer's purchase price divided by an annuity factor (interest rate 3.5%, 5 years) to give an equivalent annual cost (EAC). EAC was divided by 12 months and multiplied by 9 to give an equivalent cost of the 9-month timeframe. The purchase price of personal protective equipment (such as goggles and glasses) were included at full cost since it is not believed these would have the same durability as the device itself. We did not include in the analysis any costs for repairs or replacement devices required due to malfunction or damage, because if participants reported a faulty device during the trial, a replacement device was issued instead of repairing the existing device; in practice, repairs would be

more likely. We do, however, report in Table 19 the mean number of NB-UVB devices used over the 9 month treatment period to show that malfunction of the devices was low. The price of the device was varied in sensitivity analysis and thus the uncertainty surrounding the cost of the device (including any replacement or repairs) that would change the conclusions of the study was explored. The number of devices received per participant over the course of the trial was recorded and reported descriptively to indicate the level of faults experienced in the trial.

Participants received training in how to use the device correctly, through practical demonstration, written instructions and a video. The time spent by investigators delivering this training was captured in the CRF.

As these devices are not routinely prescribed currently in the NHS, it is unclear how they would be rolled out if they were to be adopted. In the analysis we assume the devices are given to patients at hospital appointments within the dermatology department and once returned at 9 months given to a new patient.

Topical Corticosteroid

Participants receiving the TCS intervention were supplied with two 90g tubes of mometasone furoate 0.1% ointment (Elocon® 0.1% Ointment, Merck Sharp & Dohme, Hertford). The cost of the TCS was sourced from the Prescription Cost Analysis for 2017[57] and had the National Average Discount Percentage of 7.37% (https://www.nhsbsa.nhs.uk/prescription-data/understanding-our-data/financial-forecasting) deducted and the professional pharmacist fee of £1.29 added, assuming in practice that a single tube would be prescribed at any one time.

Where participants requested additional ointment, this was recorded and costed at the individual participant level.

Whichever intervention group participants were in, it was assumed that in practice all participants would see a dermatologist at 0, 3, 6, and 9 months and these were costed even though they will essentially cancel each other out between treatment arms.

Side effects requiring medical attention from either the NB-UVB device or TCS were recorded in the CRF. These unscheduled contacts were costed using published unit costs.

Unit costs

All resource use relevant to the NHS perspective, including wider NHS usage due to vitiligo, was valued using UK unit costs (in £Sterling) for the 2017 price year (the most recent price year available

at the start of the analysis). Unit costs were identified from published sources, such as Unit Costs of Health and Social Care[58], Prescription Cost Analysis[57] and NHS Reference Costs (Department of Health, 2017). A table of unit costs, together with their sources, is presented in the Results section.

Personal costs incurred by participants as out of pockets costs due to their vitiligo were valued using patient reported estimates. These were not adjusted to reflect the year in which they were incurred since timing is likely to have had a negligible effect on price for the types of items reported (for instance, the majority of items were sun creams, emollients or camouflage products that are (or similar to products) also available on prescription and the NIC per item in the Prescription cost analysis barely changed between 2016 and 2017 – from £8.34 in 2016 to £8.29 in 2017)[5659].

Total costs

The cost of all reported resource use (relevant to an NHS perspective) was calculated for each participant. These figures were then summed for each participant, giving a total cost over the 9-month treatment period in the primary analysis. For each of the different intervention arms, a mean cost per participant was estimated.

4.4 Identification of outcome(s)

Vitiligo Noticeability Scale

The primary clinical outcome measure in the HI-LIGHT trial is participant reported treatment success, measured at 9 months, using the VNS[43]. Treatment success, a binary outcome, is defined by whether the participant responds that their target vitiligo patch is “a lot less noticeable” or “no longer noticeable” in response to the question: "Compared to the start of the study, how noticeable is the vitiligo now?". No previous studies have compared the treatments being compared in this study, hence the use of single study-based estimates of effectiveness.

Quality of Life

Quality Adjusted Life Years (QALYs) were estimated in secondary analyses using utility scores obtained from the EQ-5D-5L instrument for participants aged 11 years and over and the CHU-9D in the analysis focussed on children under the age of 18 years.[60, 61] For participants aged 5-6 years old, the CHU-9D was completed by parental proxy, but for all other ages these instruments were self-completed.

The decision to use the EQ-5D-5L was based on the EUROQOL EQ-5D-Y user guide (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-Y_User_Guide_v1.0_2014.pdf) available

at the time of study design, which stated that although the EQ-5D-Y "is generally recommended" the adult version might be possible. We chose to use just the one version of the EQ-5D in the study for consistency and because the EQ-5D-Y does not currently have a UK valuation set. The CHU-9D was chosen over the EQ-5D-Y because a UK valuation set exists for it.

Neither generic utility instrument had been used in this disease area before. Therefore their inclusion was somewhat experimental, seeking to start to build up some evidence as to their potential for use in vitiligo.

Measurement of outcome(s)

Utility measurements were collected in person at clinic visits at baseline and 9 months and via online/postal questionnaire at 21 months.

4.5 Valuation of outcome(s)

In the cost utility analysis, the responses received on the quality of life instruments was converted to utility scores using the EQ-5D-5L Crosswalk[62] UK preference weights in the base case analysis; this is in line with current recommendations[63, 64]. The CHU-9D was valued using the UK value set[58]. Following this, the utility values were used to calculate the number of quality adjusted life years (QALYs) generated over the trial treatment period of 9 months and for sensitivity analyses over the treatment and follow-up period of 21 months, using both linear interpolation and area under the curve analysis with and without baseline adjustment[65]. Separate cost-utility analyses report the incremental cost per QALY based on the EQ-5D-5L responses (for participants aged 11 years and over) and the CHU-9D responses (for participants aged 5-17) from an NHS perspective. The impact of using different preference weights for the EQ-5D-5L was explored in sensitivity analyses.

4.6 Economic analysis

All analyses were conducted in Stata MP4 version 15. The economic base-case analysis was performed on the full analysis set, where, in line with that undertaken for the primary statistical analysis, multiple imputation was used to account for missing primary outcome data and cost data at 9 months. The final analysis was a within-trial analysis, taking a 9-month time horizon in the base case analysis. As the time horizon being evaluated is 9 months in the base case costs and benefits were not discounted.

The main base case analysis was a cost effectiveness analysis, meaning decision makers will need to make a value judgement about the acceptable value of the cost per treatment success. The cost

effectiveness analysis was chosen as the primary analysis because it enabled the whole sample to be analysed together, irrespective of the participant's age. There was also some concern that available generic utility instruments may not be able to fully capture the health-related quality of life aspects of people living with vitiligo. Further details for this choice are discussed in section 4.15.

The secondary objective to assess cost utility analysis, combined estimated mean costs and QALYs for each intervention option for the two comparisons of interest with a feasible range of values for decision makers willingness to pay (λ), to obtain a distribution of net benefits for different levels of λ. In secondary analyses, the reported economic analysis used a cost-effectiveness threshold of £20,000 per QALY.

Mean (SD) resource use per participant was estimated for each randomised group. Mean difference (95% CI) in mean resource use between arms (NB-UVB only to TCS only; and combination treatment compared with TCS only) is presented. Mean (SD) cost per participant is estimated for each randomised group. Mean difference (95% CI) in mean cost between arms (NB-UVB only to TCS only; and combination treatment compared with TCS only) is estimated unadjusted.

The primary outcome for the economic evaluation is cost per treatment success.

The secondary outcome for the economic evaluation is quality-adjusted life years (QALYs) of participants over 9 months in the base case. Mean (SD) utility and mean (SD) QALYs per participant per randomised group is presented, and mean difference (95% CI) in utility and QALYs between arms (NB-UVB only to TCS only; and combination treatment compared with TCS only) is estimated unadjusted and adjusted.

Base case analyses took account of missing data and are presented unadjusted and adjusted for age and target patch. The primary economic analysis, using the clinical outcome, used the imputation model and output of the primary clinical analysis presented in chapter 3. Other analyses employed multiple imputation with chained equations using MI impute in STATA generating 60 (m=60) datasets using predictive mean matching and separately by treatment allocation, the approach reported in Faria et al[66]. Costs were adjusted for age and location of target patch as were QALYs in addition to adjusting for baseline utility using seemingly unrelated regression (SUR)[67].

4.7 Sampling uncertainty

Since costs and outcomes were skewed, non-parametric bootstrapping was used to determine the level of sampling uncertainty surrounding the mean ICERs by generating 10,000 estimates of incremental costs and benefits. These estimates were plotted on a cost-effectiveness plane. In addition, Cost-Effectiveness Acceptability Curves were produced, which show the probability each intervention arm is cost effective at different values of willingness to pay.

4.8 Subgroup analysis/Analysis of heterogeneity

Other than doing separate pre-planned secondary analysis based on the different utility instruments used (EQ-5D-5L and CHU-9D), no subgroup analyses were undertaken.

4.9 Sensitivity analyses

Sensitivity analyses were undertaken to explore key uncertainties around important parameters in the economic evaluation.

1. **Impact of missing data** was explored by comparing base case results using multiple imputation to a complete case analysis.

2. **Cost of the NB-UVB device**: the cost effectiveness of the interventions is likely to be significantly driven by the cost of the NB-UVB device. There is uncertainty about how the device would be prescribed and used, if it were found to be effective and adopted by the NHS. The base case analysis annuitised the device cost assuming that the device would be used for a period of 5 years but there is uncertainty surrounding this period of use and in practice the devices may not be returned by patients at the end of treatment. We estimate the device price at which a decision would switch from being cost effective to cost ineffective.

3. **Wider cost perspective**: As part of the trial participants were asked about the costs (if any) incurred by themselves or their families in terms of out of pocket costs as a result of their vitiligo. These costs will be added to the base case results to see if they would change the conclusions reached when considering only NHS costs.

4. **Impact of adherence**: Given any clinical effectiveness found and low adherence (defined as less than 75% adherent), the economic analysis wasl repeated including only the adherent sample, where adherence was estimated as total sessions used divided by total expected sessions.

5. **Longer-term analysis**: If either comparison was found clinically effective at 9 months, then the cost effectiveness and cost utility analyses would be repeated at the 21 months follow-up point should the completion rate of follow-up data facilitate this. Though interventions will have stopped

post 9 months, it might be useful to explore the longer-term cost effectiveness of the comparators of interest beyond this point to see if value for money (if found at 9 months) is sustained. In any sensitivity analyses taking a 21-month time horizon, costs and benefits in months 13 to 21 would be discounted using the recommended rate of 3.5% for both costs and benefits.[56] It is expected that the majority of costs and benefits would be captured in this period, and therefore it is not considered necessary to develop a decision-analytic model.

This chapter has been written in line with CHEERS reporting quality guidelines. Any deviations from the Health Economics Analysis Plan (HEAP) are described and justified in the results section below.

4.10 Results

Table 18 presents the unit costs (UK£2017), their source and any assumptions used throughout the economic analysis.

Table 18 Unit Costs Table (UK£ sterling, 2017)

Resource Item	Unit Cost (£2017)	Source (notes)
Intervention resources		
Annuity factor	4.515 based on r = 3.5% and n = 5	Drummond et al.[52]
Purchase price	149.00	Dermfix Ltd website
Annuitised 9-month purchase price[a]	24.75	(Purchase price divided by annuity factor to give equivalent annual cost (EAC). EAC divided by 12 months and multiplied by 9.)
Annuitised 9-month quality assurance (£17.83 multiplied by annuity factor)	2.96	Quality assurance: Medical Physics, Nottingham University Hospitals
Glasses (per set)	15.00	Dermfix Ltd website
Goggles (per set)	7.00	Dermfix Ltd website
TCS (per 90g tube of mometasone furoate 0.1%)	12.13	Health and Social Care Information Centre Prescription Cost Analysis[57]
Investigator face to face and telephone support (per minute, assumed band 7 £54 per hour)	0.90	PSSRU 2017 [58]
Dermatologist Face to face first appointment consultant-led	159.00	NHS Schedule of Reference Costs [68]
Dermatologist Face to face follow-up appointment consultant-led	129.00	NHS Schedule of Reference Costs [68]
Dermatologist telephone appointment consultant-led	100.00	NHS Schedule of Reference Costs [68]

Primary Care resources (per visit)		
GP	37.00	PSSRU 2017 [58]
Practice Nurse	10.85	PSSRU 2017 [58]
Pharmacist (assumed to be a community pharmacist)	11.11	PSSRU 2017 [58]
Hospital Doctor	53.33	PSSRU 2017 [58]
Hospital Nurse	15.00	PSSRU 2017 [58]
Therapist	27.00	PSSRU 2017 [58]
Other (reported by participants)	Range from 15.00 to 86.00	PSSRU 2017 [58] and NHS Schedule of Reference Costs [68]
Other Resources		
Medication (Various, NIC per item less NADP plus professional fee)	Range from 3.37 to 36.92	PCA 2017[57]
Participant and family out of pocket costs	Various	Estimates reported by participants

4.11 Intervention costs

The intervention costs consisted of the device plus consumables costs, drug costs, dermatologist appointments, training and unscheduled visit/telephone costs. We did not include the costs of training the nurses to deliver the training session with participants or of developing the video as these were assumed to be sunk costs.

Glasses and goggles were given out for eye protection when using the NB-UVB device. These were costed for the actual number given out to participants (See Table 20 and Table 22 for mean number used by group): some requested more than one set if their vitiligo patch was in a difficult to reach place or if they needed help because they were a child.

Quality assurance – the process of setting up and checking the quality of devices before they were issued to patients was estimated using expert opinion from staff at the Nottingham University Hospitals medical physics department. The quality assurance process involved device in and device out processes. Before devices were issued to participants they were tested for electrical safety and output, spectral characterisation was undertaken, and some data administration was involved. When devices were returned, they again had their output tested and some data administration was involved. Table 19 shows the time and cost for each aspect. Staff time was assumed to be a mid-point band 5 on Agenda for Change and the batch size was assumed to be 10 devices at once. Quality assurance costs were also multiplied by the annuity factor to gain the cost over the study period. In reality, quality assurance might be undertaken more frequently than every 5 years or may be provided using a different service model (e.g. specialist versus local sites undertaking the activity) which may affect cost but the impact of this assumption is tested in the sensitivity analysis section, where price is varied to see the impact on cost per treatment success.

It was assumed that devices would be given to patients at an appointment with the dermatologist. It was assumed they would have four visits with a dermatologist over the 9-month treatment period whichever treatment group they were in. Those receiving the NB-UVB would also have had an appointment with a nurse in the dermatology department and a training session with the nurse. Table 20 and Table 22 show that training time was a mean of 73.08 minutes in the NB-UVB only group and 69.17 minutes in the combination treatment group. In addition to routine visits to the dermatologist and nurse at set intervals, unscheduled contacts were also recorded. Such visits could either be face to face or over the telephone and occurred due to side-effects or concerns over the use of treatments. The number of such contacts were low in all groups, although the combination treatment group had the most (See Table 20 and Table 22).

Table 19 Quality assurance process (time and costs) for NB-UVB devices

Device out	Set-up time per batch (mins)	Cost of set-up per device (£)	Time per device (mins)	Cost per device (£)	Total cost
Electrical safety testing	10	0.52	5	2.58	3.10
Output testing	20	1.03	8	4.13	5.17
Spectral characterisation	30	1.55	10	5.17	6.72
Data administration	5	0.26	5	2.58	2.84
Device in	Set-up time (mins)	Cost of set-up (£)	Time per device (mins)	Cost per device (£)	Total cost
Output testing	20	1.03	8	4.13	5.17
Data administration			5	2.58	2.58

Those participants receiving active TCS received two 90g tubes of mometasone furoate 0.1% ointment at the outset of the study and any requests for further tubes were recorded and costed accordingly and similar amounts were requested in the TCS only and combination treatment (See Table 20, Table 21 and Table 22)

4.12 Resource use, costs and primary clinical outcome

Use of resources for the intervention and wider health care resource use related to vitiligo are shown in Table 20 and Table 22 using available case data. These show that wider health care resource use (primary care, secondary care and medicines) used for vitiligo but beyond those required for the intervention were not significantly different between groups. Vitiligo patients can be seen to be low users of NHS health care, perhaps because there is a lack of treatments currently available for this condition, or because the trial was offering the best treatment for the condition and so they had little need for further care. Table 21 and Table 23 display the mean resource use

per participant by treatment group using available case data. It can be seen that the overall mean cost per participant in the NB-UVB only group was £774.64 (SD 83.71) compared to £599.98 (SD 96.18) in the TCS only group, giving an unadjusted mean difference in cost of £174.66 (95% CI 152.75 to 196.66). The combination treatment group had overall mean costs per participant of £813.38 (SD 111.39); compared to the TCS only group this gave an unadjusted mean difference of £213.40 (95% CI 188.33 to 238.46) per participant. These figures suggest that the costs of the interventions are not offset by reductions in wider health care resource use related to vitiligo, and that if the interventions are to be considered cost-effective, the additional cost of the interventions needs to be justified in terms of additional benefit attained.

Table 20 NB-UVB compared to TCS: mean (Standard Deviation) resource use according to intervention arm over the 9-month treatment phase for all participants (based on available data)

	NB-UVB only (n=169)		**TCS only (n=173)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Intervention					
NB-UVB intervention*	1.08	0.30 (169)	0.00	0.00 (173)	1.083 (1.04 to 1.13)
Glasses	1.41	0.58 (169)	0.00	0.00 (173)	1.41 (1.33 to 1.50)
Goggles	0.46	0.60 (169)	0.00	0.00 (173)	0.46 (0.37 to 0.54)
TCS	0.00	0.00 (169)	2.15	0.55 (173)	-2.15 (-2.23 to -2.07)
Training time (mins)	73.08	40.47 (169)	0.00	0.00 (173)	73.08 (67.03 to 79.13)
Dermatologist time (clinic + telephone)	4.00	0.00 (169)	4.00	0.00 (173)	0.00 (0.00 to 0.00)
Nurse time (clinic + telephone)	2.00	0.00 (169)	0.00	0.00 (173)	2.00 (2.00 to 2.00)

Unscheduled clinic with Nurse	0.03	0.20 (169)	0.01	0.11 (173)	0.02 (-0.02 to 0.05)
Unscheduled telephone with Nurse	0.46	0.95 (169)	0.39	0.87 (173)	0.07 (-0.13 to 0.26)
Unscheduled clinic with dermatologist	0.04	0.20 (169)	0.02	0.13 (173)	0.02 (-0.01 to 0.06)
Unscheduled telephone with dermatologist	0.03	0.20 (169)	0.02	0.17 (173)	0.01 (-0.03 to 0.05)
Primary Care and Community					
Number	0.17	0.64 (132)	0.12	0.44 (136)	0.06 (-0.07 to 0.19)
Secondary Care					
Number	0.20	0.61 (132)	0.48	4.47 (136)	-0.28 (-1.05 to 0.49)
Other					
Medication	0.08	0.35 (133)	0.12	0.50 (138)	-0.04 (-0.14 to 0.06)
Out of pocket purchases	0.28	0.88 (137)	0.40	1.44 (141)	-0.12 (-0.40 to 0.16)

* Includes number of NB-UVB devices only.

Table 21 NB-UVB compared to TCS: mean (Standard Deviation) costs and outcomes according to intervention arm over 9-month treatment phase (UK£Sterling, 2017) for all participants (based on available data)

	NB-UVB only (n=169)		**TCS only (n=173)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Intervention					
NB-UVB Device	24.75	0.00 (169)	0.00	0.00 (173)	24.75 (24.75 to 24.75)

Quality assurance for device	2.96	0.00 (169)	0.00	0.00 (173)	2.96 (2.96 to 2.96)
Glasses	21.21	8.74 (169)	0.00	0.00 (173)	21.21 (19.91 to 22.52)
Goggles	3.19	4.18 (169)	0.00	0.00 (173)	3.19 (2.56 to 3.81)
TCS	0.00	0.00 (169)	26.08	6.67 (173)	-26.08 (-27.09 to -25.07)
Training time	65.77	36.42 (169)	0.00	0.00 (173)	65.77 (60.32 to 71.22)
Dermatologist (clinic + telephone)	546.00	0.00 (169)	546.00	0.00 (173)	0.00 (0.00 to 0.00)
Nurse (clinic + telephone)	72.00	0.00 (169)	0.00	0.00 (173)	72.00 (72.00 to 72.00)
Unscheduled clinic with Nurse	0.53	3.64 (169)	0.21	1.93 (173)	0.32 (-0.29 to 0.94)
Unscheduled telephone with Nurse	8.34	17.53 (169)	7.16	16.30 (173)	1.19 (-2.41 to4.79)
Unscheduled clinic with dermatologist	5.34	25.78 (169)	2.24	16.89 (173)	3.11 (-1.52 to 7.73)
Unscheduled telephone with dermatologist	2.96	20.20 (169)	1.73	16.96 (173)	1.22 (-2.74 to 5.19)
Total cost of intervention	**753.06**	**59.16 (169)**	**583.42**	**29.59 (173)**	**169.64 (159.73 to 179.56)**
Primary Care and Community					
Cost	5.90	22.20 (132)	3.90	15.21 (136)	2.00 (-2.56 to 6.57)
Secondary Care					

Cost	9.30	30.05 (132)	11.05	77.14 (136)	-1.74 (-15.90 to 12.42)
Other					
Medication	1.49	7.06 (133)	2.48	10.52 (138)	-0.99 (-3.14 to 1.16)
Total mean cost per participant	**774.64**	**83.71 (131)**	**599.98**	**96.18 (132)**	**174.66 (152.75 to 196.56)**
Out of pocket costs	4.94	20.09 (137)	14.44	96.78 (141)	-9.49 (-26.11 to 7.12)
Primary outcome					
VNS	27 (21.95)		20 (16.81)		7 (5.14)

Table 22 Combination treatment versus TCS: mean (Standard Deviation) resource use according to intervention arm over the 9 month treatment phase for all participants (based on available data)

	Combination treatment (n=175)		**TCS only (n=173)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Intervention					
NB-UVB intervention*	1.07	0.30 (175)	0.00	0.00 (173)	1.07 (1.03 to 1.12)
Glasses	1.50	0.56 (175)	0.00	0.00 (173)	1.50 (1.41 to 1.58)
Goggles	0.40	0.56 (175)	0.00	0.00 (173)	0.40 (0.32 to 0.48)
TCS	2.12	0.49 (175)	2.15	0.55 (173)	-0.03 (-0.14 to 0.08)
Training time (mins)	69.17	34.51 (175)	0.00	0.00 (173)	69.17 (64.01 to 74.33)

Dermatologist time (clinic + telephone)	4.00	0.00 (175)	4.00	0.00 (173)	4.00 (4.00 to 4.00)
Nurse time (clinic + telephone)	2.00	0.00 (175)	0.00	0.00 (173)	2.00 (2.00 to 2.00)
Unscheduled clinic with Nurse	0.13	0.51 (175)	0.01	0.11 (173)	0.12 (0.04 to 0.20)
Unscheduled telephone with Nurse	0.66	1.29 (175)	0.39	0.87 (173)	0.28 (0.04 to 0.51)
Unscheduled clinic with dermatologist	0.10	0.43 (175)	0.02	0.13 (173)	0.09 (0.02 to 0.15)
Unscheduled telephone with dermatologist	0.05	0.27 (175)	0.02	0.17 (173)	0.03 (-0.01 to 0.08)
Primary Care and Community					
Number	0.12	0.55 (142)	0.12	0.44 (136)	.002 (-0.12 to 0.12)
Secondary Care					
Number	0.20	0.63 (142)	0.48	4.47 (136)	-0.28 (-1.03 to 0.46)
Other					
Medication	0.09	0.34 (141)	0.12	0.50 (138)	-0.03 (-0.13 to 0.07)
Out of pocket purchases	0.31	1.27 (144)	0.40	1.44 (141)	-0.09 (-0.41 to 0.23)

*Includes number of NB-UVB devices only.

Table 23 Combination treatment versus TCS: mean (Standard Deviation) costs and outcomes according to intervention arm over 9-month treatment phase (UK£Sterling, Price Year) for participants (based on available data)

	Combination treatment (n=175)		**TCS only (n=173)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Intervention					
NB-UVB Device	24.75	0.00 (175)	0.00	0.00 (173)	24.75 (24.75 to 24.75)
Quality assurance for device	2.96	0.00 (175)	0.00	0.00 (173)	2.96 (2.96 to 2.96)
Glasses	22.46	8.34 (175)	0.00	0.00 (173)	22.46 (21.21 to 23.70)
Goggles	2.80	3.90 (175)	0.00	0.00 (173)	2.80 (2.22 to 3.38)
TCS	25.71	5.99 (175)	26.08	6.67 (173)	-0.37 (-1.70 to 0.97)
Training time	62.25	31.06 (175)	0.00	0.00 (173)	62.25 (57.61 to 66.90)
Dermatologist (clinic + telephone)	546.00	0.00 (175)	546.00	0.00 (173)	546 (546.00 to 546.00)
Nurse (clinic + telephone)	72.00	0.00 (175)	0.00	0.00 (173)	72.00 (72.00 to 72.00)
Unscheduled clinic with Nurse	2.41	9.53 (175)	0.21	1.93 (173)	2.20 (0.75 to 3.66)
Unscheduled telephone with Nurse	12.30	23.92 (175)	7.16	16.30 (173)	5.14 (0.82 to 9.46)

Unscheduled clinic with dermatologist	13.27	55.45 (175)	2.24	16.89 (173)	11.03 (2.37 to 19.70)
Unscheduled telephone with dermatologist	5.14	26.84 (175)	1.73	16.96 (173)	3.41 (-1.33 to 8.15)
Total cost of intervention	**792.06**	**94.61 (175)**	**583.42**	**29.59 (173)**	**208.64 (193.82 to 223.46)**
Primary Care and Community					
Cost	2.84	14.09 (142)	3.90	15.21 (136)	-1.06 (-4.52 to 2.40)
Secondary Care					
Cost	8.52	26.87 (142)	11.05	77.14 (136)	-2.53 (-16.05 to 11.00)
Other					
Medication	1.20	6.09 (140)	2.48	10.52 (138)	-1.28 (-3.30 to 0.75)
Total mean cost per participant	**813.38**	**111.39 (136)**	**599.98**	**96.18 (132)**	**213.40 (188.33 to 238.46)**
Out of pocket costs	6.62	28.45 (144)	14.44	96.78 (141)	-7.81 (-24.37 to 8.75)
Primary outcome					
VNS – No. successful (% successful)	34 (26.56)		20 (16.81)		14 (9.75)

4.13 Primary Economic Analysis

Cost effectiveness analysis of NB-UVB only compared to TCS only

The unadjusted risk difference for NB-UVB compared to TCS was 3.64% (adjusted 5.20%), this equates to a number needed to treat (NNT) of 27 (19 adjusted); in other words, 27 (19) participants would need to be treated for one of them gain treatment success.

The incremental difference in cost was £174.65 (95% CI 152.75 to 96.55) unadjusted or £173.44 (95% CI 150.55 to 196.32) adjusted for age and body region of target patch. The unadjusted incremental cost was £4,801.92 (£3,335.74 adjusted) per additional successful treatment. Figure 9 shows the probability that NB-UVB only is cost-effective at different possible levels of willingness to pay for an additional treatment success; probability increases as willingness to pay increases. It can be seen that there is a lot of uncertainty surrounding the decision as to whether NB-UVB alone, compared to TCS alone, represents value for money as there is always at least 40% probability of making the wrong decision if choosing to fund NV-UVB alone below a threshold value of willingness to pay of £10,000 per additional treatment success.

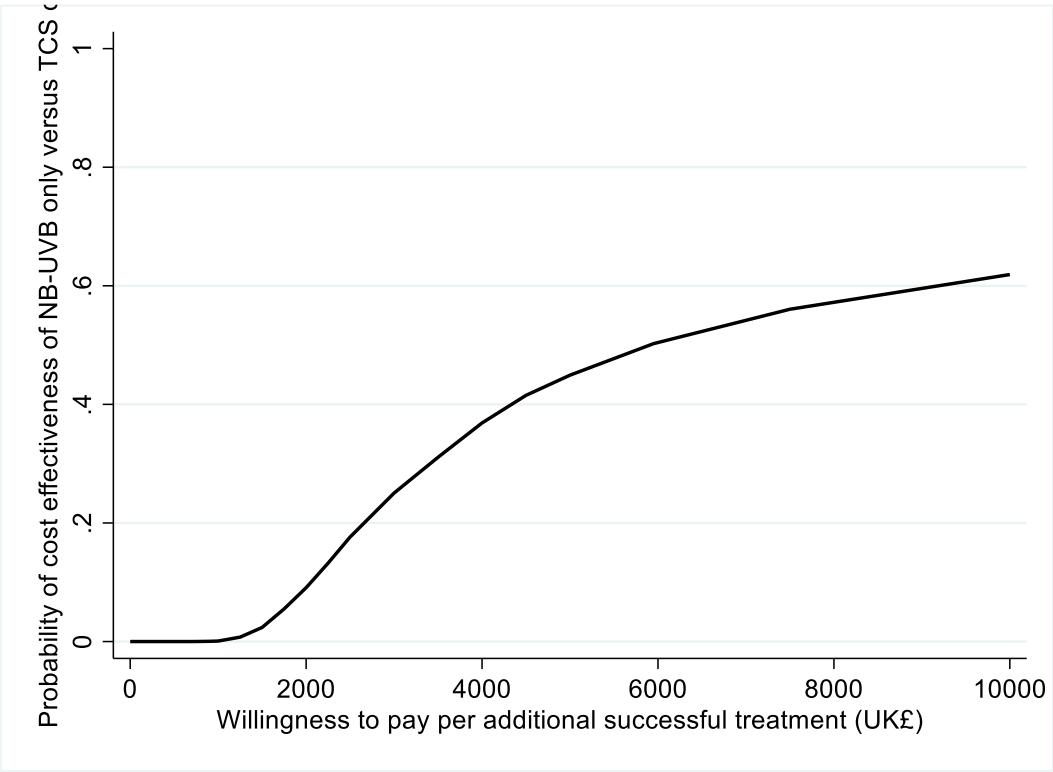

Figure 8 Cost effectiveness Acceptability curve for NB-UVB only versus TCS only

Cost effectiveness analysis of combination treatment compared to TCS only

The unadjusted risk difference for combination treatment compared to TCS was 9.16% (adjusted 10.94%). This equates to a number needed to treat (NNT) of 10 (9 adjusted) i.e. 10 (9) participants would need to be treated for one of them to gain a treatment success.

The incremental difference in cost was £213.40 (95% CI 190.02 to 236.78) unadjusted or £211.46 (95% CI 188.10 to 234.81) adjusted for age and location of target patch. The unadjusted incremental cost was £2,328.56 (£1,932.35 adjusted) per additional successful treatment.

Figure 2 shows the probability that combination treatment is cost-effective at different possible levels of willingness to pay for an additional treatment success. It shows that combination treatment is likely to be cost effective if the decision maker is willing to pay more than around £3,000 per additional treatment success. There is, however, currently no evidence to indicate how much a decision maker would be willing to pay for an additional treatment success as defined in this study. Should the decision makers willingness to pay per additional treatment success be low (i.e. less than £2,500) then it can be seen that uncertainty surrounding the decision to fund combination treatment is high.

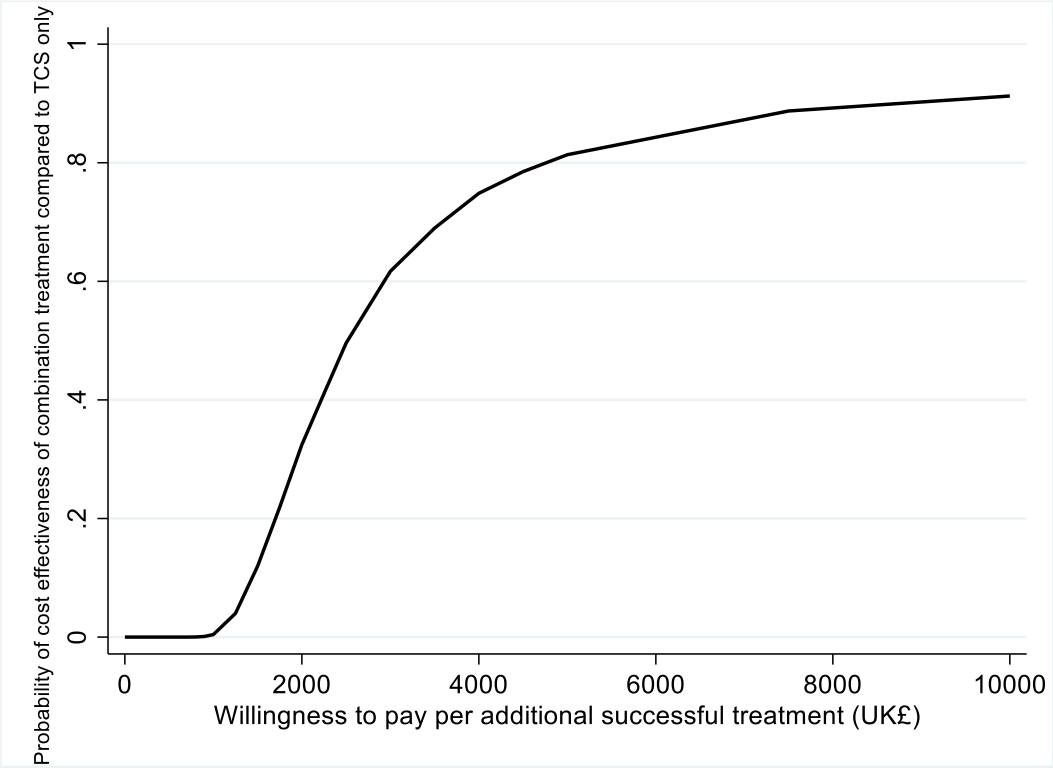

Figure 9 Cost Effectiveness Acceptability Curve for combination treatment versus TCS only

Sensitivity Analysis

A number of sensitivity analyses were undertaken to explore key uncertainties around important parameters in the economic evaluation. The results of this are summarised in Table 24 with greater detail below for each analysis.

Table 24 Summary of sensitivity analyses (adjusted results)

	NB-UVB only versus TCS only			Combination treatment versus TCS only		
Analysis	Incremental costs	Incremental effect (Risk difference)	Incremental cost per treatment success	Incremental costs	Incremental effect (Risk difference)	Incremental cost per treatment success
Primary imputed	£173.44	5.20%	£3,335.74	£211.46	10.94%	£1,932.35
Complete case	£172.61	4.88%	£3,535.40	£212.59	9.96%	£2,134.11
Cost of device zero	£121.79	5.20%	£2,342.35	£158.54	10.94%	£1,448.82
Cost of device doubled	£225.02	5.20%	£4,327.78	£264.33	10.94%	£2,415.55
Wider cost perspective	£163.90	5.20%	£3,152.30	£200.95	10.94%	£1,836.31
Adherent patients only	£193.34	13.87%	£1,393.98	£230.83	20.06%	£1,150.65

Complete case analysis

The base case assumed data to be missing at random and undertook imputation to allow for this[66]. Table 24 presents the results for a complete case analysis which only includes participants with complete resource use and outcome data in order to see if this changes the conclusions reached in the base case analysis. Three hundred and forty eight participants had complete data on both cost and outcome (success of treatment) – 113 in TCS only, 115 in NB-UVB only and 120 in combination treatment.

The cost of the NB-UVB device

The cost effectiveness of the interventions is likely to be driven significantly by the cost of the NB-UVB device. There is uncertainty about how the device would be prescribed and used within the NHS. If adopted as an effective treatment, patients may have to pay for the device themselves (with training, support and quality assurance paid for by the NHS), or the device might be adopted and provided free at point of use by the NHS for NHS patients. The base case analysis annuitised the device cost, assuming that the device would be used for a period of 5 years, but there is uncertainty surrounding this period of use and in practice it may be that the devices are not returned by patients at the end of treatment.

We re-estimated the incremental cost per successful treatment assuming that patients paid for the device, quality assurance, glasses and goggles as one extreme and at the other we doubled the price of the device, quality assurance, goggles and glasses to provide an upper estimate.

As expected (see Table 23), reducing the cost of devices to zero reduced the incremental cost per treatment success, thereby lowering the amount an NHS decision maker would have to be willing to pay for this treatment to be implemented in the NHS. Conversely, doubling the cost of the device increased the incremental cost per treatment success and meant that the NHS would have to value a treatment success more highly than the base case to be willing to adopt the treatments.

Changes in the price of the device had less impact on the combination treatment comparison to TCS only, due to the greater treatment success observed in the combination group. As noted in the primary base case analysis, it is not clear how much a decision maker would be willing to pay to achieve one more additional treatment success as measured on the VNS. Therefore, these figures just provide a range around the likely cost per treatment success.

Wider cost perspective

As part of the trial, participants were asked about the out of pocket costs (if any) incurred by themselves or their families as a result of their vitiligo. These costs were added to the base case results (NHS perspective only) to see how they would impact on the incremental cost per treatment success. Forty-seven (11.1%) of participants reported incurring out of pocket costs during the 9-month treatment period: 17 in TCS only, 17 in NB-UVB only and 13 in the combination group. The mean number of items and mean cost per participant by group can be seen in Table 20 to Table 22. The type of items included (from most to least purchased), camouflage / makeup, sun cream and sun care, clothes/scarves, face creams / moisturisers / emollients, fake tan / tanning products, travel for appointments, private appointment including multivitamins, and herbal remedies.

Taking into account the participant out of pocket costs in relation to vitiligo reduced the incremental cost per treatment success, as these costs were higher in the standard care arm (TCS only) (see Table 23 for results).

Impact of Adherence

Since significant clinical effectiveness was found and a little under half of the participants used the treatment for over 75% of the expected duration, the primary economic analysis was repeated including only the adherent sample, where adherence was estimated as total sessions used divided by total expected sessions. 227 participants adhered to treatments >75% of the time; this sample was used as the adherent sample, minus 3 participants (1 of whom had the primary outcome missing and 2 whom had cost data missing).

The intervention was more cost-effective for patients who adhered to treatment, as they were the ones most likely to achieve a successful outcome (see table 23 for estimates).

Longer term analysis (12 to 21 months)

In the health economic analysis plan we intended to explore the longer-term cost effectiveness of the comparators of interest beyond the 9 months treatment period (if either were found effective), to see if value for money was sustained. In the trial, only 30.4% of participants had complete data on NHS resource use in months 10-21, 44.5% of participants aged 11 or over completed the EQ-5D -5L at 21 months, and 43.3% of participants aged under 18 at beginning of the study had completed the CHU-9D at 21 months. Given the sparsity of data we have not performed an economic evaluation over the longer-term follow up as it would be too speculative. However, we report mean estimates of the participant's (all ages, n=517) wider NHS use over months 10 to 21 (the follow-up period) and utility at 21 months. Only 157 participants had complete resource use data for the whole 12 month follow-up period (which may have been for zero use), 64 had nine months of data available, 56 had six months of data available, 59 had three months worth of data available and 181 had no resource use data recorded for the follow-up period. The mean quarterly NHS cost per participant over the 12 month follow-up period was £21.26 (sd 46.32) for combination treatment (n=114), £25.89 (sd 52.82) for NB-UVB alone (n=117), and £21.74 (sd 42.33) for TCS alone (n=105). The mean prescription cost per participant over the 12 month follow-up period was £14.82 (sd 45.22) for combination treatment (n=114), £13.78 (sd 45.63) for NB-UVB alone (n=117), and £13.20 (sd 51.44) for TCS alone (n=107). The mean out of pocket cost per participant over the 12 month follow-up period was £42.85 (sd 398.74) for combination treatment (n=114), £3.62 (sd 16.93) for NB-UVB alone (n=117), and £8.48 (sd 39.41) for TCS alone (n=107).

Mean utility (EQ-5D-5L) per participant aged 11 or over at 21 months was 0.856 (sd 0.230) for combination treatment (n=73), 0.865 (sd 0.231) for NB-UVB alone (n=61), and 0.833 (sd 0.274)for TCS alone (n=69). Mean utility (CHU-9D) per participant (aged under 18 years at the outset of the study) at 21 months was 0.938 (sd 0.054) for combination treatment (n=20), 0.941 (sd 0.056) for NB-UVB alone (n=16), and 0.937 (sd 0.118)for TCS alone (n=16)).

4.14 Secondary Economic Analysis

Cost utility analysis for those aged 11 and over

Of the 517 participants in the trial, 456 (88%) participants were aged 11 or over, 155 were randomised to TCS only, 148 were randomised to NB-UVB only and 153 were randomised to combination treatment.

The cost utility analysis was planned as a secondary analysis due to the fact that, to our knowledge, no prior study had utilised the EQ-5D-5L, or CHU-9D for children, in patients with vitiligo. There were some concerns that such generic quality of life instruments might not be appropriate for this condition, as much of the effect may be visual or psychological rather than on physical quality of life. Such concerns seem to have be borne out in the study, Table 25 shows the domains on the EQ-5D selected by participants at baseline. 55% of participants reported having no problems on any of the five domains of the EQ-5D at baseline, suggesting that over half of the sample started the study in perfect health as defined by this instrument. This is a large ceiling effect that was also observed at subsequent follow-up (Table 25). No floor effect was observed at any time point.

Table 25 Distribution of responses over the levels of the different domains of the EQ-5D-5L

Levels	Mobility No. (%)	Self-care No. (%)	Usual activities No. (%)	Pain/ Discomfort No. (%)	Anxiety/ Depression No. (%)	No. in health state 11111 (55555)
Baseline						
1 (no problems)	416 (91.8)	436 (96.3)	394 (87.0)	376 (83.0)	292 (64.5)	55.0%
2	22 (4.9)	8 (1.8)	41 (9.1)	44 (9.7)	108 (23.8)	

3	9 (2.0)	4 (0.9)	7 (1.6)	22 (4.9)	40 (8.8)	
4	4 (0.9)	1 (0.2)	6 (1.3)	7 (1.6)	5 (1.1)	
5 (unable to/ extreme)	0 (0)	1 (0.2)	2 (0.4)	1 (0.2)	6 (1.3)	(0%)
Blank	2 (0.4)	3 (0.7)	3 (0.7)	3 (0.7)	2 (0.4)	
9 months						
1	271 (90.0)	290 (96.4)	271 (90.3)	249 (82.7)	215 (71.4)	59.8%
2	19 (6.3)	6 (2.0)	16 (5.3)	29 (9.6)	55 (18.3)	
3	9 (3.0)	3 (0.7)	9 (3.0)	18 (6.0)	22(7.3)	
4	1 (0.3)	1 (0.3)	3 (1.0)	4 (1.3)	5 (1.6)	
5	0 (0)	0 (0)	1 (0.3)	1 (0.3)	4 (1.3)	(0%)
blank	1 (0.2)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	
Final assessment (19 or 21 months)						
1	131 (64.5)	180 (88.7)	192 (94.6)	173 (85.2)	153 (75.4)	50.3%
2	50 (24.6)	14 (6.9)	2 (1.0)	21 (10.3)	36 (17.7)	
3	19 (9.4)	3 (1.5)	0 (0.0)	3 (1.5)	9 (4.4)	
4	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	2 (1.0)	
5	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	0%
blank	2 (1.0)	4	7	4	3 (1.5)	

Table 26 Unadjusted Utility and QALYs for participants aged 11 and over (available case data, primary Cost utility analysis)

	NB-UVB only (n=148)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Van Hout et al 2012 utility value set known as the 'crosswalk'					
Secondary outcomes					
EQ-5D-5L Baseline	0.8920	0.1866 (140)	0.9172	0.1145 (151)	-0.0252 (-0.0607 to 0.0102)
EQ-5D-5L 9 months	0.9287	0.1422 (89)	0.8843	0.1666 (97)	0.0444 (-0.0006 to 0.0894)
QALYs at 9 months	0.6871	0.0913 (89)	0.6721	0.0983 (97)	0.0150 (-0.0125 to 0.0425)
	Combination treatment (n=153)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Secondary outcomes					
EQ-5D-5L Baseline	0.8906	0.1719 (147)	0.9172	0.1145 (151)	-0.0266 (-0.0599 to 0.0066)
EQ-5D-5L 9 months	0.9182	0.1325 (98)	0.8843	0.1666 (97)	0.0339 (-0.0086 to 0.0764)
QALYs at 9 months	0.6843	0.0993 (96)	0.6721	0.0983 (97)	0.0122 (-0.0159 to 0.0402)

Cost utility analysis for participants aged 11 years and over for NB-UVB only compared to TCS only

The unadjusted mean cost per participant in the NB-UVB only treatment group (n = 131) was £774.64 (SD 83.71, 95% CI 760.17 to 789.11) compared to £599.99 (SD 96.18, 95% CI 583.43 to 616.55) for the TCS only group (n = 132) giving an unadjusted mean incremental cost per participant of £174.65 (95% CI 152.75 to 196.55). The imputed, adjusted, and bootstrapped mean incremental cost per participant was £169.58 (95% CI 165.50 to 173.65) more for the NB-UVB only treatment group than the TCS only group.

The imputed, adjusted, and bootstrapped mean incremental QALYs gained were 0.0204 (95% CI 0.0180 to 0.0229) in favour of the NB-UVB only compared to TCS only (See Table 26). The adjusted incremental cost per QALY was £8,293.88.

Cost utility analysis for participants aged 11 years and over for combination treatment compared to TCS only

The unadjusted mean cost per participant in the combination treatment group (n = 136) was £813.38 (SD 111.39, 95% CI 794.49 to 832.27) compared to £599.99 (SD 96.18, 95% CI 583.43 to 616.55) for the TCS only group (n = 132) giving an unadjusted mean incremental cost per participant of £213.40 (95% CI 188.33 to 238.46). The imputed, adjusted, and bootstrapped mean incremental cost per participant was £203.93 (95% CI 199.39 to 208.47) more for the combination treatment group than the TCS only group.

The imputed, adjusted, and bootstrapped mean incremental QALYs gained were 0.0145 (95% CI 0.0123 to 0.0167) in favour of the combination treatment compared to TCS only (See Table 26). The adjusted incremental cost per QALY was £14,081.

Alternative utility value sets were tested to see if they had any impact on the results but because the size of QALY gains were so small in this study (Appendix 6) the choice of value set did not affect the results presented above in the cost utility analysis.

Cost utility analysis for under 18's

One hundred and nineteen participants were aged under 18 years of age, 40 received TCS only, 39 NB-UVB only and 40 combination treatment. Complete cost and outcome data were only available for 91 (75.8%) of these participants. The results presented here are based on a complete case analysis only, as an imputed, adjusted analysis was not possible due to the small sample size. Table 27 shows the utility, as measured on the CHU-9D at baseline, 9 months, and QALYs for the 9 month treatment period. The incremental QALYs were non-significantly different from zero.

The ceiling effect on this instrument was better than the EQ-5D-5L but still high; 30% of participants had no problems according to any of the nine dimensions on the CHU-9D (Table 27). The domains of worry, tiredness and sleeping were those in which problems were reported most often.

Table 27 Distribution of responses over the levels of the different domains of the CHU-9D (number (%) of participants)

Level	Worry	Sad	Pain	Tired	Annoyed	Schoolwork	Sleep	Routine	Activities
Baseline									
1 (no problems)	91 (75.8)	109 (90.8)	104 (86.7)	67 (55.8)	104 (86.7)	97(80.8)	90 (75.0)	110 (91.7)	106 (88.3)
2	20 (16.7)	7 (5.8)	13 (10.8)	30 (25.0)	11 (9.2)	20 (16.7)	20 (16.7)	6 (5.0)	6 (5.0)
3	5 (4.2)	2 (1.7)	2 (1.7)	10	2 (1.7)	0 (0.0)	6 (5.0)	3 (2.5)	3 (2.5)
4	1 (0.8)	0 (0.0)	0 (0.0)	6 (5.0)	2 (1.7)	0 (0.0)	2 (1.7)	0 (0.0)	1 (0.8)
5 (very problematic)	2 (1.7)	1 (0.8)	0 (0.0)	5 (4.2)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	1 (0.8)
Blank	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.7)	1 (0.8)	2 (1.7)	1 (0.8)	1 (0.8)	3 (2.5)
Number in health state 111111111 (555555555)									30.0% (0.0%)
9 months									
1 (no problems)	83 (88.3)	88 (93.6)	84 (89.4)	42 (44.7)	86 (91.5)	81 (86.2)	66 (70.2)	82 (87.2)	83 (88.3)
2	8 (8.5)	4 (4.3)	9 (9.6)	25 (26.6)	5 (5.3)	10 (10.6)	17 (18.1)	7 (7.4)	3 (3.2)
3	0 (0.0)	1 (1.1)	0 (0.0)	19	2 (2.1)	0 (0.0)	8 (8.5)	2 (2.1)	3 (3.2)
4	1 (1.1)	0 (0.0)	0 (0.0)	4 (4.3)	0 (0.0)	2 (2.1)	1 (1.1)	2 (2.1)	2 (2.1)
5 (very problematic)	1 (1.1)	0 (0.0)	0 (0.0)	3 (3.2)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (2.1)
Blank	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)
Number in health state 111111111 (555555555)									29.8% (0.0%)
21 months									

1 (no problems)	48 (92.3)	47 (90.4)	47 (90.4)	26 (50.0)	32 (61.5)	44 (84.6)	41 (78.8)	49 (94.2)	46 (88.5)
2	2 (3.8)	3 (5.8)	4 (7.7)	18 (34.6)	8 (15.4)	6 (11.5)	7 (13.5)	2 (3.8)	4 (7.7)
3	1 (1.9)	1 (1.9)	0	4 (7.7)	1 (1.9)	2 (3.8)	4 (7.7)	1 (1.9)	1 (1.9)
4	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
5 (very problematic)	1 (1.9)	1 (1.9)	1 (1.9)	2 (3.8)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blank	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number in health state 111111111 (555555555)									36.5% (0.0%)

Table 28 Unadjusted Utility and QALYS for under 18's (available case data)

	NB-UVB only (n=39)		**TCS only (n=40)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Secondary outcomes					
CHU-9D Baseline	0.9450	0.0635 (35)	0.9506	0.0528 (40)	-0.0056 (-0.0324 to 0.0212)
CHU-9D 9 months	0.9538	0.0416 (28)	0.9513	0.0523 (31)	0.0025 (-0.0223 to 0.0273)
QALYs at 9 months	0.7154	0.0312 (28)	0.7135	0.0392 (31)	0.0019 (-0.0167 to 0.0205)
	Combination treatment (n=40)		**TCS only (n=40)**		**Mean difference (95% CI)**
	Mean	**Std dev (n)**	**Mean**	**Std dev (n)**	
Secondary outcomes					
CHU-9D Baseline	0.9326	0.0605 (39)	0.9506	0.0528 (40)	-0.0180 (-0.043 to 0.0074)
CHU-9D 9 months	0.9318	0.0590 (35)	0.9513	0.0523 (31)	-0.0195 (-0.0471 to 0.0080)
QALYs at 9 months	0.6988	0.0443 (35)	0.7135	0.0392 (31)	-0.0147 (-0.0353 to 0.0060)

NB-UVB compared to TCS: cost utility analysis for participants aged less than 18 years old (Table 27)

For those participants with complete cost and utility data, the unadjusted mean cost per participant in the NB-UVB only treatment group (n = 28) was £769.01 (SD 79.58, 95% CI 738.16 to 799.87) compared to £597.51 (SD 49.31, 95% CI 579.43 to 615.60) for the TCS only group (n = 31). The unadjusted mean incremental cost per participant of £171.50 (95% CI 137.35 to 205.65The unadjusted incremental cost per QALY was ££92,381.98. This figure is significantly higher than accepted threshold values and thus would not be considered cost-effective.

Combination treatment compared to TCS: cost utility analysis for participants aged less than 18 years old

For those participants with complete cost and utility data, the unadjusted mean cost per participant in the combination treatment group (n = 35 was £818.4723.94 (SD 91.20102.92, 95% CI 787.159.12 to 849.8058.77) compared to ££597.51 (SD 49.31, 95% CI 579.43 to 615.60) for the TCS only group (n = 31). The unadjusted mean incremental cost per participant of £220.965.27 (95% CI 184.23 to 257.69). Since mean cost was higher for the combination treatment group and QALYs less (albeit by a very small amount), it is possible to say that for this group of participants standard care (TCS only) dominates – that is, it is both cheaper and more effective than combination treatment. However, one should note the small sample sizes.

4.15 Discussion

This chapter has presented the results for the first full economic evaluation of treatments for vitiligo, and uses standard care of TCS as the comparator. The additional cost of the combination treatment was not offset by NHS cost savings but did result in significant treatment success over the 9 month treatment period which could be gained if decision makers were willing to pay more than the unadjusted incremental cost of £2,328.56 (£1,932.35 adjusted) per additional successful treatment (as defined in this study by 'a lot less noticeable' or 'no longer noticeable' on the Vitiligo Noticeability Scale). NB-UVB alone was less costly than combination treatment but also less effective such that the incremental cost per successful treatment was higher than for combination treatment, suggesting that the NHS would get better value for money from combination treatment than light therapy alone.

This study also suggests that patients with vitiligo do not use NHS services for their condition very much. This may be because the range of treatments available is limited and the condition is often viewed by some as being cosmetic, making people with vitiligo feel that there is not much help available.

We undertook the cost effectiveness analysis as the primary analysis because it enabled us to analyse all participants together, irrespective of age. We also had a prior belief that available generic utility instruments may not be able to fully capture the health-related quality of life aspects people living with vitiligo experience. This seems to have been borne out with a high ceiling effect on the EQ-5D-5L, where 55% of participants were in the health state 11111 (perfect health) at the beginning of the study. Although there was less of a ceiling effect on the CHU-9D, with 30% of

participants in the best possible health state, in nearly a third of children there was no capacity to measure any gain using these instruments. Those with less than perfect health reported problems in terms of anxiety/depression, pain and discomfort; and with usual activities. Undertaking the cost utility analysis gave slightly contradictory results to the clinical and cost effectiveness results, in that NB-UVB only appeared more cost effective than combination treatment for those aged 11 and over, whilst neither treatment arm appeared cost effective for the under 18's sample using the CHU-9D (although this probably reflects the small sample size for this age group). The cost utility results are not that useful, and likely reflect a lot of uncertainty around the QALYs gained as the gain between groups was effectively very close to zero in both comparisons. Therefore, more weight should be attached to the clinical effectiveness results and further work to explore the measurement properties of the EQ-5D and CHU-9D in this patient group is warranted, given the high ceiling effect observed in this study. A number of sensitivity analyses were undertaken, and these suggest that perspective, cost of the NB-UVB light device, and method of dealing with missing data do not change the conclusions reached. Repeating the analysis including only adherent participants does not change the overall conclusions either, although in this case the results do suggest that if it were possible to predict which individuals were likely to be adherent to treatment, the cost per treatment success for this group would be lower than the base case as they have a higher probability of success.

New treatments such as Janus Kinase (JAK) inhibitors are currently being developed as a novel treatment for vitiligo, especially for those with more extensive skin involvement. Although these treatments show some initial signs of promise, they are likely to be very costly when they become available within healthcare systems. The relatively lower costs of the interventions assessed in this trial may therefore be advantageous when resources are limited, and the trial has yielded useful cost-effectiveness data which can be used for comparison with these novel treatments.

4.16 Conclusion

Combination treatment has a lower incremental cost per successful treatment than NB-UVB only but whether this is considered cost-effective will depend on the judgement of healthcare decision makers regarding how much they are willing to pay to achieve a successful treatment. The fact that vitiligo has few treatment options available, and the likely high cost of newer treatments being developed, may be important to consider in this regard.

Chapter 5: Process evaluation

5.1 Introduction

The clinical effectiveness (or otherwise) of home-based interventions for vitiligo is only one factor in determining whether such interventions will eventually be implemented across the NHS. This chapter considers the health economic impact of home-based provision; here we explore the process of intervention delivery and the experience of managing treatment at home. Understanding how treatments are experienced, and unpicking the opinions of those involved in providing them (in the trial and potentially in future clinical services), will help us to navigate and interpret the HI-Light clinical and economic findings. It will also help us to generate better informed recommendations for future clinical practice; recommendations which are supported by the subjective experience and preferences of those affected by vitiligo.

This focus has pertinence for home-based light treatment as neither dermatology nor primary care services currently routinely prescribe hand-held (home-based) NB-UVB for any dermatological condition. New services would need to be commissioned and designed. Should such provision be initiated it would necessarily involve the provision of relatively expensive equipment for long-term domestic use. Although TCSs are already being prescribed for vitiligo, potent TCSs are prescribed mainly in secondary care, whereas in primary care, lower-potency TCSs tend to be used, and for shorter time periods. Clinicians and patients recognise that both NB-UVB and potent TCSs may have potentially harmful side effects. Moreover, the complexity of treatments delivered in combination, side-effect monitoring and routine dose adjustment might all influence how well home-based treatment is accepted and integrated within personal and domestic circumstances. How this complexity is managed in the HI-Light trial might also inform the nature and scope of future clinical supervision and the support that is made available for future home-based treatment.

At the outset, a programme theory (Box 1) was described, which outlines how home-based treatment for vitiligo might work in ideal circumstances. Although informed by prior development work and a pilot trial[24], the programme theory, by its very nature, includes a number of speculative or idealistic assumptions. Home-based treatment for vitiligo is viable when "*clinicians and commissioners consider vitiligo to be a condition that warrants treatment*" and when patients "*decide that they wish to receive treatment for their vitiligo"*. Clinicians and commissioners need to *"understand their role in the pathway to making these treatments available to patients"* and patients need to be "*happy to receive this treatment"* (for both treatment options). That patients should not

be "*overburdened or confused by using both treatments concurrently*" is important, and patients should be "*able to access support from the medical professionals as required*". Previous research might suggest that achieving all these criteria can be challenging[24].

Aims and objectives

The aim of this process evaluation is to generate insight from a range of stakeholders which will support the interpretation of HI-Light clinical and cost effectiveness data and inform the generation of recommendations for future clinical practice.

Specific objectives include:

- To contextualise clinical and cost effectiveness data with subjective reports of the experience of home-based therapy.
- To consider whether stakeholders (patients, clinicians and commissioners) view home-based treatment for vitiligo to be acceptable and feasible.
- To identify difficulties with the delivery and management of home-based treatment for vitiligo.
- To consider implementation issues associated with the future delivery of home-based treatment for vitiligo.

The process evaluation will use qualitative and quantitative data to *test* the programme theory and inform recommendations for the future delivery of home-based treatment for vitiligo.

5.2 Methods

Study Design

This is a mixed methods process evaluation incorporating stakeholder interviews, interviews with NHS commissioners, an online survey of those who delivered home-based treatment in the trial and focus groups with those who delivered the trial.

Ethical approval was obtained for the process evaluation on 10th April 2017 (Ethics reference 14/EM/1173, SA04) from NRES Committee East Midlands – Derby.

Participants

(i) Trial participants were recruited from the main HI-Light Vitiligo trial.

Sampling was purposive, focussed initially on age, treatment allocation, recruiting site and treatment success (based on the primary outcome). Other factors, such as treatment adherence, early stopping of treatment, ethnicity/skin type, gender, extent of vitiligo, number of patches being treated, and whether the participant experienced problems with treatment, guided later stage recruitment of interviewees.

Participants were approached at the 9-month time-point to minimise impact on treatment adherence.

(ii) Commissioners were identified via online directories of Clinical Commissioning Groups (CCG) and via personal contact with members of the study team.

(iii) Upon completion of the trial, site investigators (principle investigators and research nurses) at all recruiting centres were invited to take part in an online survey and/or a focus group to review the delivery of NB-UVB

To avoid any impact on recruitment to the trial, all activities with recruiting site staff were conducted after recruitment had finished.

HI-Light – How Home-based treatment for vitiligo might function in the NHS.

[This document describes the ideal situation for a person with vitiligo who is seeking treatment within the NHS]

Initial consultation in primary care

A patient visits their GP because they are concerned about pale patches on their skin. The GP correctly diagnoses vitiligo. The GP is aware that vitiligo is treatable and is knowledgeable about all possible management options and recognises the importance of early treatment. After a discussion about the physical and psychological impact of their vitiligo and the possible management options, the patient decides they wish to receive treatment for their vitiligo. The GP is supportive and offers to prescribe a potent topical corticosteroid and manage within primary care if appropriate, and/or offers referral to a dermatologist. The GP also refers the patient for other relevant services such as camouflage and psychological support as required and provides advice on sun protection.

Topical corticosteroids (TCS)

The GP or dermatologist prescribes TCS on an intermittent regimen to avoid side-effects and the patient is happy to receive this treatment. A healthcare professional fully educates the patient on the use of TCS (including information on frequency of application, amount to be used, and sites to avoid e.g. the genital area) and prescribes the TCS for as long as is required to achieve the desired outcome. The patient feels empowered to use the TCS, is aware the treatments are slow acting but is prepared to stick to the recommended duration and frequency of application. The patient is willing and able to return for regular follow up visits for monitoring of side effects and efficacy. The patient experiences no side effects from the TCS. If after 3 months of TCS there is no beneficial effect, the treatment is stopped. If there is a beneficial effect, the TCS is continued for up to a year, with regular follow up. The TCS is stopped once the vitiligo is completely cleared.

Hand-held narrow-band (NB) UVB light therapy

The dermatologist prescribes hand-held NB-UVB. The patient is happy to receive this treatment and is able to commit sufficient time to use the device. A phototherapy service is available and home phototherapy is supported. A medical professional with a full understanding of how to use hand-held NB-UVB for vitiligo fully educates the patient on the use of hand-held NB-UVB (including treatment regimen). The patient feels empowered to use the hand-held NB-UVB device. The patient is then given a hand-held NB-UVB device which has been checked for output and safety to take home. The patient is aware the treatments are slow acting but is prepared to stick to the recommended duration and frequency of application despite it taking a significant amount of time each day and is able to treat all patches of vitiligo without experiencing any problems with the regimen or the device. The patient is willing and able to access support from the medical professionals as required. The patient is willing and able to return for regular follow up visits for monitoring of side effects and efficacy. If after 3 months of NB-UVB there is no beneficial effect, the treatment will be stopped. If there is a beneficial effect, the NB-UVB is continued for up to a year, with regular follow up. The NB-UVB is stopped once the vitiligo is completely cleared.

Combination treatment of topical corticosteroids (TCS) and hand-held narrow-band (NB) UVB light therapy

Combination treatment of TCS and hand-held NB-UVB is considered to be the most appropriate treatment option for this patient so a dermatologist prescribes these as above. The patient is not overburdened or confused by using both treatments concurrently.

Service provision / clinician perspective

Clinicians are able to diagnose vitiligo and recognise the importance of early treatment. Clinicians and commissioners consider vitiligo to be a condition that warrants treatment. They are willing to offer hand-held NB-UVB and/or TCS therapy for vitiligo to all suitable patients. Both clinicians and commissioners understand their role in the pathway to making these treatments available to patients. Clinicians have the knowledge, skills and resources required to prescribe these treatments, train patients in using them, and to ensure the hand-held NB-UVB devices are correctly maintained. Support services are available including medical physics, phototherapy and medical photography.

Box 1 Underpinning Programme Theory

Data collection

(i) Semi-structured interviews were carried out with those trial participants who consented to this element of the study.

Interviews lasted between 30 and 60 minutes in duration; they were conducted by telephone or video call. All data was recorded using digital audio recording equipment and interviews were transcribed in full by a professional transcription service.

Interviews focused upon experiences of participating in the trial, perceptions of treatment, and views on whether treatments should be available to more people with vitiligo. Topic guides were used to structure the interviews, and participants were encouraged to focus upon (or introduce) any topic they felt important.

Participants were offered a £20 gift voucher to compensate for their time if they participated in an interview.

Participants provided consent were asked to sign an online consent form before the interview, however, if it was not possible to obtain consent in this way, verbal consent was obtained prior to the interview commencing in line with the ethical approval.

(ii) Interviews with commissioners were similarly guided by a semi-structured topic guide. Interviews with commissioners were shorter, approximately 20-30 minutes.

They were also delivered via telephone or video call and recorded using digital recording equipment. Data was transcribed in full.

(iii) An online survey (see Appendix 7) was delivered to all recruiting centre staff via the Survey Monkey online survey software. Questions considered the challenge of delivering NB-UVB and sought insight and recommendations about the nature and form of any future implementation of NB-UVB in the treatment of vitiligo.

The survey was live between 25th March and 24th April 2019.

Following the online survey, site investigators were invited to a one-day 'results' meeting where progress in the HI-Light trial was presented (29th May 2019). At this meeting participants took part in short focus group discussions (60 minutes) as well as whole group discussion of the trial findings. Discussions were guided by semi-structured topic guide (Appendix 15) with each focus group facilitated by experienced facilitator.

All discussion at this meeting was audio recorded and transcribed in full

Data analysis

(i) Data was anonymised and handled using the NVivo software package (QSR International, Warrington, UK) for qualitative data analysis (version 12).

Transcripts were coded following the conventions of framework analysis[69, 70] using a framework initially derived from the underpinning programme theory and set out in 3 broad matrices: experience of treatment, need for treatment, and future implementation. The coding framework was developed and amended as data suggested new insight and topics.

Coding and thematic development were checked by multiple members of the team to ensure valid and relevant interpretation.

(ii) Data was anonymised and handled using the NVivo software package for qualitative data analysis (version 12).

Data was charted to the analytic framework described above, although into separate matrices so as to distinguish commissioner data. Coding and thematic development were checked by multiple members of the team to ensure valid and relevant interpretation.

(iii) Descriptive statistics were generated for the online survey responses.

Free text responses (in the online survey) and focus group discussions were anonymised and handled using the NVivo software package for qualitative data analysis (version 12).

Again data was charted to matrices described above; site investigator data was charted to dedicated matrices to ensure that this data could be considered independently. Coding and thematic development were checked by multiple members of the team to ensure valid and relevant interpretation.

Themes across matrices for (i), (ii) and (iii) were compared, contrasted and synthesised in order to address study objectives.

5.3 Results

Data overview

(i) Twenty-five interviews with trial participants (or parents) were conducted between 13th July 2017 and 20th July 2018 (See Table 29).

Twelve out of the 16 recruiting sites were represented in the sample.

Table 29 trial participant interview characteristics

	Group	Number in sample
Age group of participants	5-11 years	10
	12-17 years	2 (+1)
	18+ years	13
Treatment group	A	10
	B	7
	C	8
Treatment success (according to primary outcome)?	Yes	9
	No	12
	No primary outcome data	4
Adherence to treatment	Completed treatment	19
	Stopped treatment early	3
	Did not attend 9-month visit	3
Ethnicity / skin type	I	0
	Ii	4
	Iii	10
	Iv	6
	V	5
Gender	M	12
	F	13
Number of patches treated	1	2
	2 to 3	10
	4 to 5	6
	6+	7
Number unscheduled visits	0	16
	1	3
	2	3

	3	3
Reported issues with using light device	Problems	10
	No problems	15

(ii) Nine commissioner interviews, involving 10 individuals, were conducted between 5th June 2017 and 10th October 2017.

Participants included strategic and operational roles in commissioning process, and represented a geographic spread across England. Most were medically trained, and included GPs with a special interest in dermatology.

(iii) Twenty-four recruiting site staff completed the online survey – seven doctors, 16 nurses and one other.

Ten of these had prior experience of phototherapy services, for others Hi-Light had been their introduction to this treatment. To support anonymity we did not collect data about which site they represented.

Thirteen site staff participated in the focus groups representing ten recruiting sites. Eleven nurses were split into two groups; two doctors formed the final focus group.

Thematic analysis

Thematic analysis is organised around three questions:

1. Can home-based treatment for vitiligo be adequately managed by HI-Light trial participants, and supported by those clinical teams involved in the trial?
2. Do stakeholders feel that home-based treatment should be made available as part of routine NHS provision?
3. Do stakeholders feel that home-based treatment for vitiligo could be integrated within current NHS organisation and pathways?

Is Home-based NB-UVB treatment and TCS for vitiligo manageable for participants?

All bar two of the (healthcare professional) survey respondents agreed that home-based treatments are 'easy' for participants; discussion group data (with site investigators) reinforced this, with healthcare professionals reporting that the phototherapy device is (superficially) simple to operate and most trial participants seemed to understand the instructions offered about light therapy and corticosteroid ointment. Trial participants offered a similar assessment indicating that they generally understood how to use the individual treatments, training and support offered by the research nurses and demonstration video had helped in this.

Some practical difficulties with individual treatments were described (by both site investigators and trial participants) but nothing of a magnitude to prevent participants effectively managing their treatments. For light therapy: timers which failed, guard teeth which broke-off, difficulties reaching

parts of the body, and difficulties using (a flat device) on curved parts of the body. For TCS ointment: an unpleasant smell, a greasy feeling, and poorly absorbed. The time commitment required for light therapy was a common cause for comment:

> *"it felt like an awful amount of time, I am pretty busy and to eventually be spending in excess of three quarters of an hour per two days just felt like an inordinate amount of time."* Adult participant 3

Treating multiple patches could leave participants feeling overburdened:

> *"I started with more than that because I was quite positive, I was doing different parts of my body like six or seven or something … Then I just did three, the three patches they were interested in so I was just treating them, no more."* Adult participant 4

Time seemed to be more of an issue for parents treating a young child (i.e. *keeping them still!*), or if there were other children in the household that required attention. Participants described linking treatment to "*treat time*" for children (such as watching television); others described building routines that facilitated their time commitment:

> *"Yes it was always around 6 o'clock after my tea and after I'd washed up and whatever you know, then I didn't have time to just sit and do it then."* Adult participant 12

> *"Yeah, so I used to sort of do each week in advance so that I knew what I'd got to do the next week and how long each treatment was going to be, and I'd put my notes next to it so I knew I'd done it, so no, I was quite comfortable with that."* Parent of child participant 3

Although time consuming, home-based phototherapy was considered less disruptive than regular hospital visits for phototherapy, and the potential for treatments at home was important to the majority of trial participants.

Despite a generally positive assessment of each treatment, healthcare professionals and some participants flagged the complexity of treatments in combination. Site investigators reported that trial participants who they thought had a good understanding of treatments made errors with TCS and phototherapy dose, and suggested that some individuals had disregarded instructions and used the ointment/device excessively on multiple body-sites. One trial participant admitted as much:

> *"I just ramped it up pretty much straight away back to what it was, but again no redness whatsoever which only really served to confirm it's a dummy."* Adult participant 11

Some trial participants said that they found the combination treatment protocol complicated, particularly early on, and expressed caution when initially using the treatments:

"Yeah I found it confusing for the first few weeks, it was like one week on one week off [for TCS]*, and every other day for the light and stuff"* Parent of child participant 5

Some trial participants acknowledged that they had made mistakes with treatment:

"I was completely knackered and was [?] at the end of the day, had done the light treatment. So, I sat and did my chest which was one the areas being treated and part of, one of my, part of my left hand which is the other bit of the treatment and then started to do the second bit on the left hand and fell asleep so I ended up burning myself" Adult participant 3

Stepping-up or down NB-UVB dose (as part of the treatment protocol or in response to erythema) was recognised to confuse and cause difficulties, with site investigators concerned that some participants never appeared to fully understand the process of incremental dose change. Trial participants indicated that their treatment diary was essential in guiding them:

"Yes, without that it would be nowhere, without the form that you fill in with boxes I mean and writing down the time you would be absolutely nowhere, there's no chance in a million that you would actually keep to anything like the protocol" Adult participant 3

A further area of complexity identified by trial participants was in assessing whether treatment was making any difference and the importance of the photographs in determining any change:

"well I thought [things had improved] *but when we got the photographs, you know we got the photographs on the computer; it didn't seem to be any different to be honest. "* Adult participant 12

"only when I went back and saw the difference in the photographs, so as I was treating it I couldn't really see any difference, when you saw the photographs versus my face in the mirror actually, there was a difference." Adult participant 5

Seasonal variation in skin tone might add to this complexity:

"because usually I do find I do get quite tanned and therefore, between the summer and winter there is a contrast, so without looking at the photographs I couldn't tell whether actually it was making any difference or not." Adult participant 5

Trial participants described nurses as having an important role in supporting them in assessing whether treatment was leading to improvement; nurses were also considered important in supporting the management of erythema (especially when it occurred for the first time). Overall, participants viewed nurse support positively:

"*they responded quickly, were helpful and friendly, they offered reassurance, and generally insured that participants were doing the right thing*."

In contrast, participants were sceptical of the potential for GP led support:

> *"In all honesty if I rang my GP up and I had an issue, they're useless anyway, you have to wait god knows how long to get an appointment and whatever else"* Parent of child participant 6

Despite the acknowledged complexity of the combination treatment trial participants reported that they felt able to adhere to treatment regimen without any fundamental difficulty. Where they had not adhered to protocol this would more often be with light therapy and participants would point to legitimate (practical) reasons for this, such as other health conditions or holidays:

> *"like I say it was literally just when we went away on holiday, I just, I probably wouldn't have done it if I did take it to be honest when I'm on holiday."* Adult participant 9

Others had not adhered to light treatment protocol when they recognised no benefit from treatment, many associated this with receiving a dummy device.

> *"I think I only really found it onerous because I was just convinced it was a dummy, and I just felt as if I was, about 20 minutes I was really just wasting basically because I thought this was not going to be any good at all"* Adult participant 11

> *"as soon as I realised that it wasn't even tanning my skin I just, it was really hard to continue because it was really time consuming"* Adolescent participant 2

These comments suggest the importance of expectations in shaping how treatments are managed – some individuals ceased treatment because expected improvement had not occurred. That noted it should be made explicit that most trial participants demonstrated generally realistic expectations, often borne out of previous treatment experience:

> *"I mean it's not like sunburn or a suntan is it, where the skin sort of changes overnight practically, if you've got something happening in the cell structure maybe that takes a much longer time because you're waiting for the cells to regenerate"* Adult participant 10

> *"6 months I would have expected to have seen something."* Adult participant 2

> *"So, it's just I didn't have great expectations, possibly because of previous treatments and stuff"* Adult participant 13

Expectations were, however, often tempered by an intuitive, emotional responses to the offer of a new treatment:

> *"I was hoping for them to shrink or bring some of the pigmentation, like away, get her back to her normal colour."* Parent of child participant 5

> *"Actually, I was very pessimistic about the whole thing but I was, I didn't really think that I was going to get any benefit"* Adult participant 13

Should Home-based treatment be made more widely available?

Although potentially complex (and confusing for some) there was a general sense that this type of combination treatment should be made available to more vitiligo patients; 18/24 HCP survey respondents *agreed* or *strongly agreed* with this. Focus groups with site investigators supported this by highlighting a clinical population that have few treatment options, and for whom the impact of vitiligo can be very distressing.

> *"We have always said that it is the best of a bad bunch of treatments, and it probably still is. There is no fantastic treatment out there for vitiligo, there doesn't seem to be, and the trial doesn't show that it's fantastic. It's shown that for patients its worthwhile doing because the quality of life is impaired for a lot of patients. They are pinning hopes on it" Site Investigator 9 – Research Nurse*

This is reflected in those reasons offered by trial participants for taking part in HI-Light. Some hoped that participation would bring them access to new treatments for themselves or their children, some subsequently hoped for complete remission, whilst others hoped that their disease would stop spreading. For a minority of participants there was a sense of "nothing to lose":

> *"had hoped it would totally recover the nine months or earlier you know, the sort of blemishes would disappear"* Adult participant 5

> *"I decided to take part because why not, it would be working on my skin or not but I just decided to take part to see what happened"* Adult participant 4

> *"I don't know, probably half and half of me was hoping that yes, something would work and it would help her, but if it didn't then we wasn't really going to lose anything"* Parent of child participant 7

Others hoped that their involvement in HI-Light would benefit the broader vitiligo population by contributing to the development of a new treatment pathway. Given these assessments it is understandable that site investigators recognised the importance of new treatments for their patient population; even suggesting that (irrespective of clinical impact) new treatments offer vitiligo patients *hope* and the potential to *engage* with their condition.

As this desire for new treatments might suggest, commissioners confirmed that treatment pathways for vitiligo are often lacking, suggesting that dermatology, let alone vitiligo, is unlikely to be a priority in commissioning discussions. They also indicated that some commissioners perceive vitiligo to be a 'cosmetic' condition, which adds a further barrier to it being considered a priority area. Variation in cosmetic impact (and associated concerns) was also manifest in comments made by trial participants, which suggests that willingness to pursue (complex) treatment might vary according to site or visibility of vitiligo:

> *"if I had, say if it was like more in a cosmetic important place I'm pretty sure I would be prepared to have a go at it long term, when saying long term, I mean over a period of years or whatever is required."* Adult participant 3

> *"I never felt that for a chap of my age, I mean I'm 74, it's a bit irrelevant because they're worse when you've got a bit of a suntan obviously, but it's not like being perhaps a lady who cosmetically can look a bit odd"* Adult participant 7

These comments illustrate and support the assessment of site investigators that home-based therapy might not be appropriate for all vitiligo patients. In the online survey 12 site investigators indicated that home-based therapy would be appropriate for *most people,* 11 indicated that it would be appropriate for *some*, but none indicated that it would be appropriate for *all* people with vitiligo. Considerations for providing home-based treatment might be (i) *clinical*, (ii) *practical*, or related to (iii) *personal circumstances*:

(i) Comments from consultant dermatologists (as part of the survey and site investigator discussions) speculated that combination treatment might be particularly beneficial for new patients as an early intervention.

Trial findings point to variation in outcome according to body site of vitiligo patch (see chapter 3).

Target patches were chosen by trial participants, and had to have been active in the preceding 12 months, as reported by participants. Discussions with site investigators suggested that some participants may not have been able to judge this very well, with some investigators feeling potential participants may have exaggerated the activity of their vitiligo in order to obtain access to the treatments offered in the trial.

(ii) The practical challenge of managing combination treatment (long-term use, dose fluctuation, potential side-effects, etc.) was recognised by both participants and site investigators. Participants suggested that not all people are sufficiently organised for these treatments; they thought that

individuals need to plan ahead, be committed to the treatments, and to be willing to incorporate them into their routine.

> *"If you're an organised type of person it becomes part of second nature after a while."* Adult participant 1

In some cases, hospital based light therapy was considered more appropriate.

> *"Yes, to go to the cabinet and spend five, ten minutes and that is all because you will have treated all your body"* Adult participant 4

The duration of home-based treatment was also a factor to be considered when considering individuals.

> *"I think doing it for any longer* [than nine months] *probably would have been a bit challenging probably, because it became, it did start to become a bit more of a hassle to do it so regularly,"* Parent of child participant 2

> *"Towards the end, I mean I really did find, it just felt like I was spending a lot of time"* Adult participant 3

Healthcare professionals felt that mental health issues, other health complaints, or significant caring responsibilities (e.g. multiple children) might all challenge an individual's ability to maintain a complex treatment regimen over a long period of time.

(iii) Beyond practical challenges there was concern from healthcare professionals that an individual's level of understanding about vitiligo and their expectations of treatment might also be important. Those with potential difficulties adhering to a long-term treatment programme may be unlikely to benefit home-based treatment, those with unrealistic expectations might find it difficult to adhere. Trial participants recognised that some individuals might exaggerate, or provide inaccurate information about patches, to gain access to a new treatment

Establishing which individuals might benefit from home-based treatment was considered difficult by healthcare providers; fully sharing information about effectiveness, treatment burden and treatment duration may help support shared decision-making. Some site investigators even suggested that some kind of test, formal or informal, of whether or not a patient understands the treatment regimen might also be appropriate.

Could Home-based treatment be made more widely available outside the trial?

A small number of site investigators indicated that they were already re-using devices from the trial and incorporating them into clinical practice for vitiligo. Indeed, some sites in the UK (e.g. Ninewells Hospital, Dundee) are already offering such devices for use at home, often to treat other skin conditions such as scalp psoriasis.

Other site investigators pointed to the importance of situating new pathways within existing phototherapy provision for other skin conditions, with appropriate support from medical physics to monitor device output. That this would not be possible in all locations was recognised and some suggested that home-based treatment should be managed regionally by specialist centres.

These perspectives mirror commissioners' concerns that any new treatment would need to sit within (or at least not disrupt) existing service pathways. In contrast to site investigators, commissioners were, however, less aware of a need for new treatment pathways and perceived no explicit demand from patients, clinicians or healthcare providers.

> *"I'm not getting any complaints for example about the services that we provide. Like GPs aren't coming to me saying, we're not happy with this. As far as our GPs are concerned, they're getting a good service because their patients aren't complaining to them. It's not coming up on our monitoring in terms of performance" MC - Commissioner*

Should a new treatment pathway be considered, commissioners stressed that clinical and cost effectiveness would be key to any decision, they warned that significant changes to services would need to be supported by considerable evidence of clinical or cost improvement.

> *"I think the only issue would be time … a change in service is something that can be time consuming. So the benefit has to be significant. So we're making an assessment how significant the change is." JB - Commissioner*

Investigators recognised that commissioners might be reluctant to commission new services and speculated upon different mechanisms for the provision of phototherapy devices.

All investigators recognised that these devices can be easily purchased online and some reported that participants had indicated that they might buy one independently of NHS support. Similarly, several participants described considering purchasing a device, although for some the thought of "going it alone" deterred them.

> "*I think they're about £100 aren't they, they're not fantastically expensive but I didn't then think I might go and buy one of those, largely because I wasn't sure how I would use it you*

know, it's very secure and comforting isn't it to have that kind of regime and do this, that and the other every day, and then you think 'right okay so I know where I'm up to' and so on, so to suddenly be cut loose from that would be a little bit more you know, anxiety provoking, when you know that it's potentially dangerous" Adult participant 6

Investigators recognised that the publication of (positive) trial findings might accelerate this type of independent use amongst a patient population desperate for treatment options. Most investigators were apprehensive about this – in the online survey only 2/24 felt NHS involvement was *not important* and 13 felt this *essential* or *very important*. Concerns for safety led some investigators to suggest that devices should be automatic (i.e. patients cannot adjust) or managed by a dermatology nurse. Some patients also suggested that devices could have safety features such as automatic cut-outs to prevent overuse. Investigators also suggested that patient monitoring should be frequent and sooner than three months (as in the trial). Some participants recognised the value of an earlier monitoring visit, whereas others felt that this was not necessary:

"*personally think it needs an interim visit, if only to compare the photograph, because I do think that you forget what it was like and you do think 'oh it's not making any difference', but then when you see the photograph and you see the shape changing*" Parent of child participant 3

The potential for some form of 'mixed economy' - where patients lease or purchase a phototherapy device within an NHS service – was considered by site investigators to be the most likely way that effective provision could be offered. However, this is not without its difficulties: both trial participants and site investigators were concerned about unequal access for those that cannot afford to purchase or lease a device; some healthcare professionals suggested that 'purchasing healthcare' might lead to unreasonable expectations and/or incorrect use (*if I'm paying for it will work!)*; and, the failure to return leased devices might make a service economically not viable (127 light therapy devices were not returned during this trial).

5.4 Discussion

It is perhaps unsurprising that data generated from multiple sources (with contrasting clinical and patient perspectives) produces a complex, and at times contradictory, set of insights.

- *Treatments which are 'easy', but which are complex in combination.*
- *Treatment which should be made available to more vitiligo patients, but where selection of patients might be essential.*

- *Treatment which might be purchased independently by patients, but which would need significant monitoring and support from the NHS.*

Through much of the process evaluation data (especially in participant and site investigator insights) there is a marked divergence between the recognised potential for home-based treatment and concerns for harm associated with its inappropriate or unsupervised use.

Trial fidelity

The process evaluation offers some insight to support the interpretation of the clinical and cost effectiveness data.

Participant interviews demonstrated that adherence to the treatments was not hampered by a lack of knowledge about how to use the treatments, nor by a lack of support when using them. Intermittent non-adherence to treatment was acknowledged (and is perhaps unsurprising given the treatment burden associated with light therapy) but these were most often a pragmatic response to life circumstances and events. Trial adherence data (Table 7) shows that around two-thirds of participants used the treatments as specified in the treatment protocol whilst they were still using them.

All of which suggests that trial procedures were adequate in supporting *normal* practice, and that clinical findings were neither inflated nor diminished by unrealistic or disastrous levels of treatment adherence.

Where trial procedures were, however, less successful was in blinding participants to treatment allocation. Trial data demonstrates that a relatively high percentage of participants stopped treatment early, with only around half using treatments for at least three-quarters of the expected duration (Table 7). Whilst some participants stopped treatment because they had achieved complete remission, more commonly participants indicated that a lack of effect led them to cease treatment with some suggesting that they knew their light device to be a dummy. A lack of any redness in the skin or other indications such as warmth meant that around half correctly guessed they had the dummy device (89% of those using active light guessed correctly).

With regard to trial outcomes, participants were largely able to judge the primary outcome (VNS). The use of photographs was crucial in this, due to the duration between visits, and/or because of difficulties in establishing whether minor changes had taken place. It is perhaps worth noting that participants indicated that *seasonal variation* in the noticeability of their vitiligo, more noticeable in summer, may have impacted upon their assessments. The consistency of other trial outcomes, however, suggests that this was not a major issue.

Population in need

Site investigators recognised a clinical population with few treatment options, commissioners acknowledged that vitiligo is not a priority area, and trial participants expressed a desire to try new treatments which might work where normal clinical practice had failed. Health economic assessment suggests that many individuals with vitiligo manage with little or no NHS input. The culmination of these insights demonstrate that there is an unmet need for effective treatments for vitiligo.

Participants were willing to go to great lengths to accommodate the time-consuming and complex treatment regimen; many were willing to continue treatment in the absence of any effect. Expectations were realistic - participants hoped for partial improvement or halting the spread of vitiligo (rather than complete re-pigmentation), few expected immediate results. These characteristics might suggest that the levels of treatment success observed in the trial, and ability of the interventions to stop the spread of vitiligo, offers sufficient potential for individuals with vitiligo to be willing to try (and persist with) home-based treatment in the future.

Assuming that vitiligo does, however, have at least some degree of psychological impact in many people with the condition, it seems important that future recipients of vitiligo treatments should be fully informed about the likely success rate of home-based treatment, to ensure realistic expectations of treatment.

Easy to do but complex to use

Site investigators and trial participants recognised that treatments were relatively straightforward to use, with appropriate instruction and support.

However, economic assessment points to the cost effectiveness of combination treatment (more so than treatments in isolation); a complex treatment protocol coupled with a considerable time burden (both each day and over a period of months) creates potential for incorrect use which can result in either increased side-effects or reduced effectiveness. Site investigators were particularly concerned about the potential for participants to harm themselves. Treatment diary planners and site staff were considered essential by trial participants in helping them to navigate this complexity. It is notable that some participants had considered purchasing a light therapy device, but had decided against this because of a lack ongoing NHS support. Site investigators stressed the importance of ongoing support and monitoring of patients in any future clinical service.

The clinical data indicate a need for some form of intermittent maintenance therapy, as effectiveness diminished once treatments had been stopped. Many trial participants were relieved

to stop light therapy after nine months, suggesting that maintenance therapy with TCS is more likely to be a preferred approach over maintenance light therapy.

Treatments may not be suitable for all

Treatment burden means that home-based therapy is less appropriate for those wishing to treat a high number of patches. Lifestyle and personal circumstances may make adhering to a complex treatment regimen over an extended period difficult for some. It is also pertinent to remember that not everyone with vitiligo wants or is seeking treatment.

Site investigators stressed the difficulty of predicting which participants were most likely to benefit from home-based treatment. Fully discussing the advantages and disadvantages, treatment burden and timescale of home-based treatments are essential in helping people with vitiligo reach informed decisions about treatment.

Integrating within the NHS

Site investigators were positive about the trial results (*any improvement is worthwhile* was a common sentiment), and participants were keen to see effective treatments for vitiligo become available. However, it is unclear whether sufficient improvement is manifest here to convince commissioners of the value of home-based phototherapy for the management of vitiligo. Home phototherapy services that support treatment of a broad range of skin conditions, as seen in existing specialist phototherapy units offering home phototherapy (e.g. Ninewells Hospital in Dundee), are likely to be more attractive.

Both site investigators and trial participants recognised that light therapy devices might be privately purchased. Some site investigators were concerned about this, and some trial participants indicated interest in privately purchasing, whilst at the same time being concerned about a lack of clinical support if they did so. It is pertinent to stress here that training, treatment diaries, technical support and staff support were all considered essential by site investigators (and many trial participants) to the success and safety of home-based treatment. Medical physics is required to ensure that devices are appropriately calibrated and to ensure that bulb output is consistent; phototherapy services are required to support a complex treatment regimen, monitor effects, and support/temper patient expectations.

The culmination of these two strands points to the potential for some form of mixed economy provision where light therapy devices are leased or privately purchased (independently or via the NHS) with treatment defined, supported and monitored by NHS services. The number of devices

(127) not returned after the end of treatment period in this trial might make NHS leasing of devices a less appealing prospect to commissioners.

Site investigators recognised that not all settings are well placed to provide medical physics support, and commissioners suggested that new pathways are more attractive if they sit within existing provision (rather than requiring infrastructure development). This might point to a hub and spoke model of regional delivery whereby specialist sites with existing medical physics expertise could provide access to home phototherapy devices across a number of NHS Trusts, but clinical provision including training and monitoring of side-effects, could be delivered locally.

It is perhaps appropriate to conclude by recognising that the challenge of any future home-based treatment for vitiligo will be in navigating the needs of patients and their enthusiasm for new treatment alongside the concerns of healthcare professionals about the potential side-effects associated with light therapy and long-term TCS use.

Study strengths and limitations

This process evaluation synthesises data from a range of relevant stakeholders to provide insight into the delivery and experience of home-based treatment for vitiligo. It complements the clinical and health economic data summarised elsewhere in this report. The subjective experiences which are reported here provide an important context to support interpretation of the clinical findings and provide situated detail to inform future service development and delivery.

The evaluation is comprehensive in its coverage, in that those exposed to home-based treatment, those that delivered it, and those that might commission it in the future were all consulted. Insight might have been enhanced further with the inclusion of more teenagers in the process evaluation, but other than this it is positive that the views of adults, young people and parents of children with vitiligo were all incorporated into data collection. It is also positive that amongst those trial participants who engaged with the evaluation some had positive experience of treatment, others less so.

As with all research of this kind we acknowledge that participants were to some extent self-selecting, and it may be that those with particularly positive or strong views about home-based treatment were more likely to consent to involvement in the process evaluation. Site investigators could potentially have a vested interest in the future commissioning of home-based treatment for vitiligo and so might be inclined to give more positive views.

As with all qualitative data, there is some degree of interpretation in our analysis of the interview and discussion group data. Whilst we have tried to ensure some rigour in this process (multiple

coders / group discussion about interpretations) there is always potential for us to misunderstand or misinterpret what we were told.

Chapter 6: Patient and Public Involvement

6.1 Background

The involvement of key stakeholders, such as patients and their carers, representatives from patient support groups, and health care professionals, is important when identifying clinical research priorities and when developing and designing clinical trials. This helps to ensure that the resulting research evidence is useful and relevant to clinical care, is delivered efficiently and recruitment targets are achieved with minimum unwarranted burden on participants.

Many of the current treatments for vitiligo have been assessed through clinical trials, but variation in the design of these studies and a lack of standardised outcome measures makes it difficult to compare the effectiveness of these treatments[71]. Systematic reviews have also shown that there is wide variation in the choice of outcome measures used in vitiligo trials[33].

In addition to the lack of standardised outcome measures and limited use of patient reported outcome measures (PROMs) in vitiligo trials, until now there has been very limited stakeholder involvement in identifying the most important areas for future vitiligo research, or in designing new vitiligo trials.

We sought to address these issues when we started to develop the HI-Light Vitiligo Trial, and here we report how we did so.

6.2 Aims

To evaluate the impact of stakeholder involvement in the design, delivery and dissemination of the HI-LIGHT Vitiligo Trial.

6.3 Methods

This work is reported using the Guidance for Reporting Involvement of Patients and Public (GRIPP2) guidelines[72]. It outlines the breadth of stakeholder activities that have contributed to the delivery of a multicentre RCT from 2009 to present, and the impact of this involvement on the design, delivery and dissemination of the HI-LIGHT Vitiligo Trial. For the purpose of this report, we use the term ‘stakeholder’ to include people with vitiligo and their carers, representatives from organisations representing people with vitiligo (e.g. patient support groups), and health care professionals who treat people with vitiligo and healthcare commissioners.

Data were collected and logged throughout the trial using the eight core principles of the Public Involvement Impact Assessment Framework (PiAFF) identified by Telford et al [73], outlined in Table 30.

Table 30 Summary of core principles for PPI involvement in the HI-Light trial

Core principles	Inclusion in the HI-Light trial
Principle 1: the roles of the stakeholder are agreed between the researchers and the stakeholders involved in the research	The role of the stakeholder representatives was documented in the funding application, protocol and final report
Principle 2: researchers budget appropriately for the costs of the stakeholder involvement in research	Stakeholder costs were included in the trial budget. Costs associated with stakeholder work throughout the trial (e.g. travel expenses, time commitments) were reimbursed.
Principle 3: researchers respect the differing skills, knowledge and experience of stakeholders	Different stakeholders (people with vitiligo and their carers, representatives from organisations representing people with vitiligo (e.g. patient support groups), and health care professionals) were involved in various aspects of the trial. Requests for involvement were tailored to each individual stakeholder group's skills, knowledge, experience and stage of the trial.
Principle 4: stakeholders are offered training and personal support to enable them to be involved in research	Patient partners invited to join the Centre of Evidence Based Dermatology's Patient Panel, which provides regular sharing of information, an annual face-to-face training day, and opportunities to attend relevant national training events and conferences.
Principle 5: researchers ensure that they have the necessary skills to involve stakeholders in the research process	Researchers involved in the HI-Light trial are experienced in the involvement of stakeholders in research and embedded within institutions that value the central role of patients and the public as partners in research.
Principle 6: stakeholders are involved in decisions about how participants are	Stakeholders were involved in the design and development of trial recruitment procedures and

both recruited and kept informed about the progress of the research	documentation. Through The Vitiligo Society in particular, stakeholders were pivotal in the communication of trial developments to both participants and the wider vitiligo community and in giving advice about recruitment.
Principle 7: stakeholder involvement is described in research reports	Stakeholder contribution and analysis of its impact included in the final report and written up as a separate paper.
Principle 8: research findings are available to stakeholders, in formats and in language that they can easily understand	Stakeholders were invited to the HI-Light results meeting in order to discuss the findings of the research from a stakeholder perspective. Lay summaries of trial findings were developed with input from stakeholders.

Details of stakeholder involvement and evidence of impact were collected on dedicated logs throughout the development and duration of the trial.

6.4 Results

Contextual factors relating to stakeholder involvement

Funding body

The HI-Light trial was funded by the National Institute for Health Research Health Technology Assessment (HTA) programme. This funding body is dedicated to the involvement of the public in the delivery of research, rather than through participation in clinical trials alone. The NIHR defines public involvement in research as 'research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them'[74].

Working in collaboration with the NIHR ensured committed funds for the involvement of the public throughout the delivery of the HI-Light trial, from the identification of the research question to the dissemination of trial results.

Research Group

Both the Centre of Evidence Based Dermatology (CEBD) and Nottingham Clinical Trials Unit (NCTU) have extensive experience in the involvement of the public in the delivery of clinical trials. The CEBD were able to utilise existing networks, including a well-established patient panel whose members

receive training and support through face-to-face workshops, newsletters and attendance at relevant training courses/conferences

Sponsor organisation

The University of Nottingham places strategic importance on the involvement of patients and the public in both teaching and research activities. A Public Engagement Lead is employed to support each faculty of the university, including the Faculty of Medicine and Health Sciences, to support researchers in developing PPI initiatives to engage effectively with PPI partners throughout project delivery.

Patient support groups

The research team had strong pre-existing links with UK based charity The Vitiligo Society.

Stakeholders involved in the HI-Light trial

Stakeholders (including people with vitiligo and healthcare professionals) were involved across all areas of trial design and delivery. They were involved in prioritising the initial research question; completing surveys to inform trial design; developing and testing the primary outcome; assisting in trial conduct, recruitment and oversight; and contributed to the analysis and interpretation of the trial results. The number and types of stakeholder involved at each stage in the trial life cycle are shown in Figure 10.

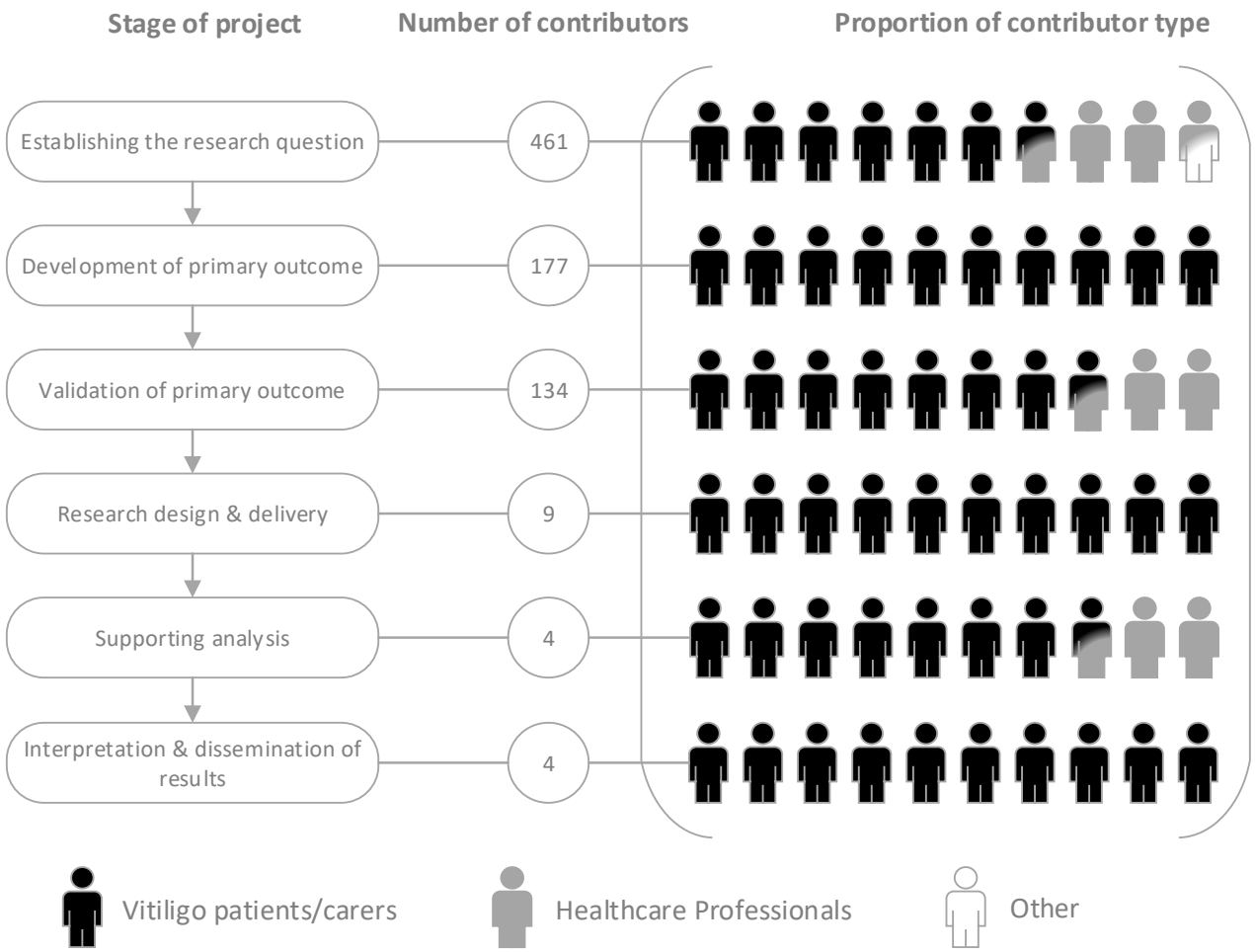

Figure 10 Stakeholder contribution to the design, development and execution of the HI-Light trial

Stages of research and opportunities for stakeholder impact

The impact of stakeholder contribution in the development and delivery of the HI-Light Trial are summarised in Table 31.

Table 31 The impact of stakeholder contributions to the trial.

Stage of the research	Methods used in the HI-Light trial	Measures of impact
Establishing the research question		
	In 2009, members of the HI-LIGHT Trial team led the Vitiligo Priority Setting Partnership in collaboration with the James Lind Alliance and The Vitiligo Society[21]. 302 people with vitiligo, 142 healthcare professionals and 17 people from other sources contributed to the survey.	The PSP identified the top priorities for future research as defined by people with vitiligo and healthcare professionals, whilst also highlighting the importance of assessing the suitability of vitiligo treatments for children. The National Institute for Health Research prioritised a commissioned research call to address two of the Top 10 research priority topics: (1) Which treatment is more effective for vitiligo: steroid creams/ointments or light therapy? (2) How effective is UVB therapy when combined with steroid creams or ointments in treating vitiligo? The HI-Light trial was designed to fit this call and recruited both children and adults to help in providing a much-needed evidence base for children with vitiligo.
Development of primary outcome measure	A systematic review was conducted to assess which outcomes are measured most frequently in vitiligo trials[33]. In parallel, a survey conducted between January and March 2009 asked people with vitiligo or	Emphasised the inconsistencies across the reporting of outcome measures in vitiligo trials and the need for standardised outcome measures.

	their carers (n=165) to suggest which outcomes should be used in future clinical trials. These two processes laid the foundation for work to identify a core set of outcomes measures, which should be captured in future vitiligo trials Three online discussion groups involving people with vitiligo (n=12) were held with an overall aim to further narrow down (i) the most important concepts when measuring treatment success and (ii) potential wording for questions to assess treatment success. As with the earlier PSP, participants for the focus groups were identified via the CEBD mailing list and through the VS.	Helped to establish the most important outcome measures in vitiligo research, including cosmetic acceptability of treatment response. Survey work amongst people with vitiligo showed that the outcome domains that are important to people with vitiligo included 'cosmetically acceptable repigmentation' and 'normal looking skin[33]'. Further work determined the most appropriate way of assessing cosmetic acceptability of treatment response contributed to the development of the VNS[43].
Validation of primary outcome measure	Work was carried out to validate the primary outcome measure (VNS) through the scoring of baseline and after treatment images by health care professionals (n = 33) and people with vitiligo (n = 101).	This work showed that (i) the VNS has good construct validity, acceptability and interpretability, supporting its inclusion as a patient-reported measure of the cosmetic acceptability of treatment response in vitiligo trials, (ii) the VNS is a better and more consistent indicator of global treatment success than percentage repigmentation, (iii) VNS scores of 4 or 5 can be interpreted as representing treatment success and (iv) further validation of the VNS is required[43].

Research design and delivery		
Trial oversight	An experienced patient researcher (MW) was a co-applicant on the grant application for the HI-Light trial, acting also as a representative of The Vitiligo Society. Another patient representative of The Vitiligo Society (MS) acted as a lay member of the Trial Steering Committee (TSC). A patient researcher (MW) joined the trial team as a co-applicant and was a regular participant in Trial Development Group meetings during the funding application process.	The presence of patient representatives on trial oversight committees was invaluable throughout the design and delivery of the trial, helping to ensure that patients remained at the forefront of trial objectives.
Trial documentation	Five patients with experience of vitiligo advised on the content and ease of use of Patient Information Sheets and treatment diaries.	Feedback was incorporated into all aspects of patient facing trial documentation to ensure that it was both meaningful and informative to vitiligo patients.
Data collection	The patient researcher (MW) advised and commented on the development of the CRF, suggesting wording changes and amendments.	Feedback from MW led to the following changes to the Case Report Form: • Suggested 'getting worse' instead of 'active'. • Questioned the meaning of 'dietary requirements'. • Suggested we try to capture information about traditional non-western medicine.

	Nine patient representatives were involved in the review and testing of the online follow-up questionnaires for the trial.	• Suggested that a visual prompt i.e. drawing of a hand and foot, rather than a descriptive prompt may help when identifying patches during follow-up appointments. There were few reported problems with the online questionnaires from trial participants, and questionnaires that were completed were comprehensive.
Recruitment and engagement activities	The patient researcher (MW) and a young person with vitiligo and her mother assisted with the recording of a video to aid recruitment, and a video demonstration of how to use the light treatment (see images 1a and 1b). These videos were used for training purposes. Site staff were encouraged to play the videos to participants at their baseline clinic appointment as a part of their intervention training. Participants were then given either a DVD of the training videos to take home, or a link that they could use to watch the videos online. The patient researcher and trial Chief Investigators gave presentations at The Vitiligo Society conferences to raise awareness of the trial. They also contributed pieces to The Vitiligo Society newsletter on an ongoing	Participants reported feeling confident in their ability to use the treatments appropriately. Interviews carried out with trial participants as a part of the trial process evaluation suggested that, alongside the participant handbook, the videos were a useful tool to assist with the treatment regime.

	basis, to update Society members about the progress of the trial and to help with trial recruitment	
Supporting analysis		
Providing blinded outcome assessment from the perspective of people with vitiligo	Blinded assessment of baseline and post-treatment digital images were undertaken by 3 lay assessors (people with vitiligo) and 1 clinical assessor.	Data provided by these blinded assessors were used to inform interpretation of the trial results.
Process evaluation		
	A subset of HI-Light trial participants and their carers were interviewed once they had completed the trial. Questions explored the patients' experiences in using the treatments and possible barriers and facilitators to their use.	Results of the process evaluation informed interpretation of the trial results and implementation planning for uptake of the treatments within the NHS.
Interpretation		
	Four people with vitiligo attended the internal trial results reveal meeting. Patient partners were involved in producing and reviewing lay summaries of the trial findings, participant newsletters and social media communications.	Having a strong patient presence at the internal results meeting ensured that interpretation of the results was appropriate and helped inform discussions around the clinical relevance of the observed treatment effects. Patient representatives also provided guidance on the delivery of trial results to the vitiligo community. Summaries of results were provided in accessible formats for multiple stakeholder groups

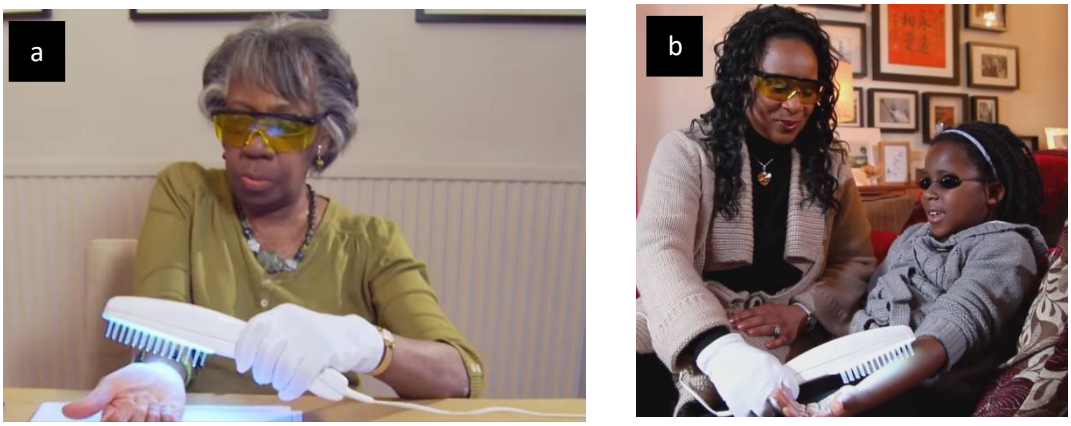

Figure 11 Stills from the HI-Light trial training videos.

A patient researcher (a) and a young person with vitiligo and her mother (b) demonstrate the use of the NB-UVB handheld light device

From stakeholder to participant

During the delivery of the HI-Light trial, the patient researcher (MW) expressed an interest in being involved as a trial participant. In such instances, care should be taken to ensure that there is a clear distinction between being a member of the trial team (in this case a patient representative) and trial participation in order to protect the blinding and to preserve the equipoise of the research team. Following discussions between the research team and the patient researcher, it was decided that the prior role as a member of the research team should cease for the duration of her involvement as a trial participant. However, our patient researcher was able to provide valuable input at the trial results meeting, where she assisted with interpretation of the results and ongoing dissemination activities.

Reflections from our stakeholders

> *I feel very privileged to have been involved with the Hi-Light project from its inception. I was impressed by the way the trial was organised and conducted which involved patients in many aspects of trial design. I took part in videos, including the (NB)UVB training video, and other forms of publicity to encourage participation in the trial. My observation that small improvements in percentage repigmentation was not meaningful for patients led to the decision to develop a new scale for use as the primary outcome measure in the trial. I also commented on the wording of all patient-related study materials and on-line questionnaires to make them easier for patients to complete and I helped to develop the VNS scale.*

Patient researcher and member of the Trial Management Group

As I have vitiligo, and have experienced the difficulties in getting access to treatment. The trial seemed to provide a bit of hope for those wanting to treat their patches. If people have an opportunity to do this kind of voluntary work, I really recommend taking it. It's been really interesting and I hope the lay volunteers have made a positive contribution to the trial overall.

Blinded image assessor

Being a vitiligo sufferer myself, I felt honoured to be asked to be part of this trial by looking at before and after treatment photos. It is exciting to see the research that is still being done and how the ways of treatment are still being explored. I would also be happy to take part in any future trials and participate in any further research.

Blinded image assessor

: *As someone with vitiligo it is always pleasing to be asked to help in research. I have a PhD in pain control based on research I did in the NHS many years ago so I know how important it is to have people willing to give their support to research projects in a committed and consistent manner – I was more than happy to help. I would hope that if the results are in favour of a treatment effect then this treatment can then be offered to more people – but it may only work for some and not at all for others so we'd need to try it and see on a case by case basis. I look forward to learning more about this and thank you for allowing me to participate as an image reviewer.*

Blinded image assessor

I was delighted to be approached and take part in this trial. I agreed to take part because a) it felt like a professionally run trial and b) my role as a trustee of a related charity.

I felt the organisation of the trial, the regular communications and reading materials were excellent. I felt part of the team and I recognised that extra effort that was made to include me in conversations/debates even though I was not a medical expert. As a senior manager in

business I was able to draw parallels with the formal board meetings and governance I have encountered in my day to day work. This felt like a series undertaking.

I felt a little energy and momentum has been lost recently but that is also a recognition of the very high standards encountered at the beginning.

Going forwards I would like to have sight of any publications relating to the research and would be delighted to support any further research relating to vitiligo.

Patient member of the Trial Steering Committee

When Ebony and I were approached to take part in the Hi-light trial, it gave us a great opportunity to be involved in research that was being undertaken in order to help those who were living with vitiligo. Both Ebony and I were happy to contribute to this trial as we believed that any outcome would be one step nearer to finding a cure for vitiligo or at least being able to manage the symptoms of living with vitiligo.

I believe that during the trial the journey was made easier from the training tape that we were allowed to follow but also from the support that we were given during this time from those involved in the trial.

Mother of child participant

Maintaining communication

A Trustee of The Vitiligo Society, who has vitiligo, actively contributed as a member of the Trial Steering Committee (TSC). This, along with the involvement of the patient researcher on the Trial Management Group, provided invaluable patient perspectives on key trial decisions. It also helped to maintain a connection between the trial management team and the community of people with vitiligo. The Chief Investigator and patient researcher attended meetings organised by The Vitiligo Society in order to keep the vitiligo community aware of trial progress and encourage participation in the trial.

6.5 Discussion

This report documents the diverse involvement of stakeholders in the development, delivery and dissemination of a large multicentre RCT. The importance of PPI and wider stakeholder involvement

in all aspects of research delivery were recognised by the trial funder, trial sponsor and research team. This shared passion helped to facilitate successful stakeholder involvement throughout the life cycle of the HI-Light trial.

We have demonstrated significant impact from stakeholder involvement, particularly in prioritising the research question, defining the primary outcome, and informing the trial design. Involving a panel of people with vitiligo in the blinded assessment of the digital images was innovative and provided reassurance that the primary outcome was not influenced by accidental unmasking of the trial participants to their treatment allocation. Involvement of a range of key stakeholders during discussion of the trial results was key to understanding the clinical relevance of the findings, which demonstrated a statistically significant, but relatively small treatment effect.

We used existing partnerships between people with vitiligo and the research team, in order to facilitate meaningful stakeholder contribution across all aspects of the trial, with almost 800 individuals contributing overall. Given the large number of children involved in the trial, it is possible that greater impact could have been made by involving young people and parents of children with vitiligo.

There was some criticism from stakeholders that communication towards the later stages of the trial was less evident and this most likely reflects the long time delay between the end of treatment at 9 months, and the end of long-term follow-up after 21 months. For trials such as this with long-term follow-up, special efforts could helpfully be made to ensure that participants and stakeholders understand the reason for apparent inactivity and delays in hearing about the study results.

6.6 Conclusion

The NIHR-funded HI-Light trial had a strong stakeholder contribution in all aspects of trial design and delivery. With invaluable input from patients, patient carers and healthcare professionals, we were able to deliver the largest multi-centre vitiligo trial to date, and have successfully developed a patient-reported outcome and used it to assess a patient-led intervention. Our working relationship with the vitiligo patient community has proven to be mutually beneficial, and one that we hope continues to grow.

Chapter 7: Device Testing

7.1 Introduction

NB-UVB treatment is usually carried out in a hospital setting, although in some countries there are well-developed systems for allowing NB-UVB treatment to be carried out at home [75]. For vitiligo, although treatment is usually administered in a hospital setting, there is increasing interest in hand-held devices, which can be used at home to deliver NB-UVB to localised areas of vitiligo[24, 76, 77]. However, there are a number of evidence and knowledge gaps in the optimum use of localised NB-UVB treatment for vitiligo[23, 24]. In particular, there is little evidence regarding the consistency of dosing delivered by localised NB-UVB units, the quality assurance measures that should be followed in their use, and whether there are any significant safety issues, especially when people with vitiligo use the units at home.

- In preparation for the main trial, a pilot study was carried out that identified potential dosimetry issues that may arise during the use of hand-held NB-UVB units, which could have possible implications for maintaining adequate control of participant NB-UVB exposure. The following potential dosimetry issues were identified:
- the absolute device output was lower than the manufacturer's specification, which has implications for defining the treatment protocol exposure times
- there was variation in device output , which could make it difficult to evaluate treatment effects
- there was a change in tube output during use, with implications for defining the treatment protocol exposure times
- short-term early life change in device output were observed, which suggests that a pre-burn of bulbs prior to delivery to a participant might be necessary.

These issues have the potential to be critically important in the context of home-based treatment, without the usual degree of control over treatment that would be achieved in a hospital-based phototherapy unit. Furthermore, we wanted to minimise potential variance in trial outcomes caused by NB-UVB dosimetry issues. Therefore, it was clear that we needed to conduct a thorough analysis of device output prior to their use in the main trial.

The aim of the work reported here was to ensure that the hand-held NB-UVB devices used in the HI-Light Vitiligo Trial delivered a consistent and safe dose for all trial participants (addressing the issues identified above), so that any variance in trial outcomes attributable to variance in the output of the

NB-UVB devices would be kept to an absolute minimum. We planned to achieve this aim using the following objectives:

1. To establish whether the device output was consistent with the outputs as specified by the manufacturer, and to quantify the variation in device output across all devices used.

2. To quantify the likely drop in output over time and establish whether a pre-burn period was necessary prior to distribution of devices to trial participants.

3. To provide quality control checks on all trial devices prior to distribution to ensure all issued devices had outputs within a pre-determined range.

4. To develop a dosing schedule for use in the trial that ensured patient safety whilst delivering a clinically useful dose of NB-UVB.

7.2 Materials and Methods

Use of NB-UVB devices in the HI-Light Vitiligo Trial

Before commencing trial recruitment, we undertook a photometric characterisation set of measurements as described in Study 1 below, in order to achieve objectives 1,2 and 4.

The Hi-Light Vitiligo Trial recruited 517 participants (children aged over 5 years and adults) who were randomised into one of three parallel groups. 425 live devices and 175 placebo devices were tested. This was more than the number of participants due to some tested devices not being suitable for participants and anticipation of some devices requiring replacement during treatment. Participants (and their carers) were recruited at 16 secondary care sites around the UK and trained in how to use the NB-UVB device by watching a training video, and receipt of a written manual during a thorough face-to-face training with a research nurse. If a participant felt that the NB-UVB device was not working properly, they reported this to the co-ordinating clinical trials unit, and a replacement unit was sent out from the central trial pharmacy. Faulty devices were returned by the participant and replaced. The faulty devices were sent back to the manufacturer.

Once the trial started recruitment, we performed the tests described in Study 2 below prior to issuing the devices, to achieve objective 3. All study tests were performed by a single team of scientists and technologists experienced in UV measurements.

Devices and test equipment

The hand-held NB-UVB device used in the HI-Light trial was the Dermfix 1000MX unit (Androv Medical, Leatherhead, UK). This unit is provided with a suggested dosing schedule, to be used after consultation with a supervising medical professional. We sought to develop a simplified dosing schedule that could be used in the trial. Initially the manufacturer supplied 10 Dermfix 1000MX units and 2 fluorescent tubes for characterisation (LightTech LTC 9W/G23 and Philips PL-S 9W/01/2P tubes). Although there were small differences in spectral emissions [differing relative intensities at equivalent wavelengths] and a reduced output from the LightTech tube, the cost differential between the tubes was felt to outweigh these emission differences and so for all further characterisation and trial utilisation, LightTech tubes were used in the hand-held devices. This is the standard configuration for this unit.

A Bentham DMc150 spectroradiometer (Bentham Instruments, Reading, UK), comprising a radiometer and double monochromator, was used to verify spectral outputs and an ILT 1700 radiometer (International Light Technologies, Peabody, MA, USA) was used for instantaneous irradiance measurements and integrated dose measurements. The spectroradiometer's double monochromator and radiometer were calibrated against a mercury lamp with traceable spectral emissions. The ILT 1700 radiometer was field calibrated against the spectroradiometer.

To ensure consistency of output measurements, a jig to hold the Bentham and ILT sensors was designed and built by the Clinical Engineering Department at Nottingham University Hospitals NHS Trust (Figure 12 and Figure 13). This ensured that the sensors were positioned over the centre of the lamp at the comb tip in order to consistently simulate desired clinical use.

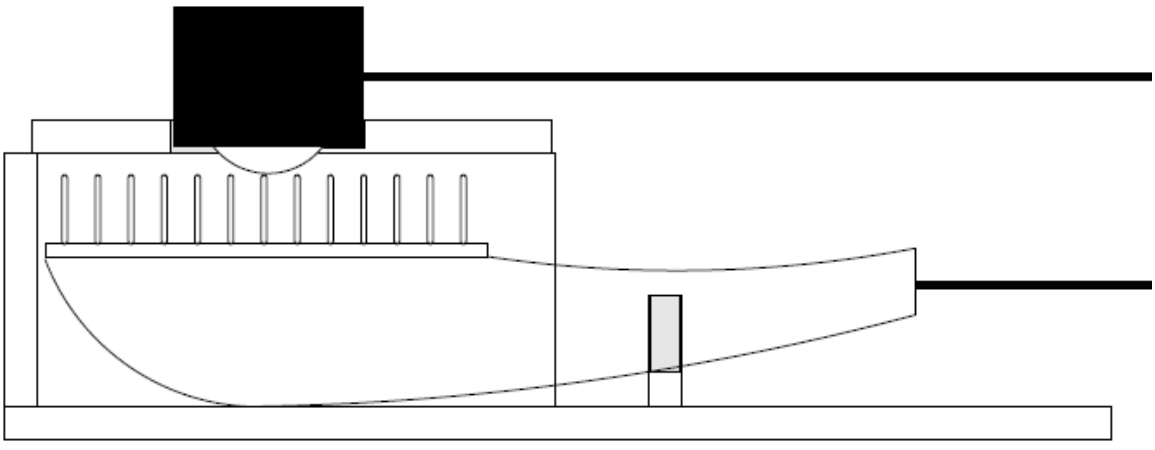

Figure 12 Elevation drawing of the measurement jig

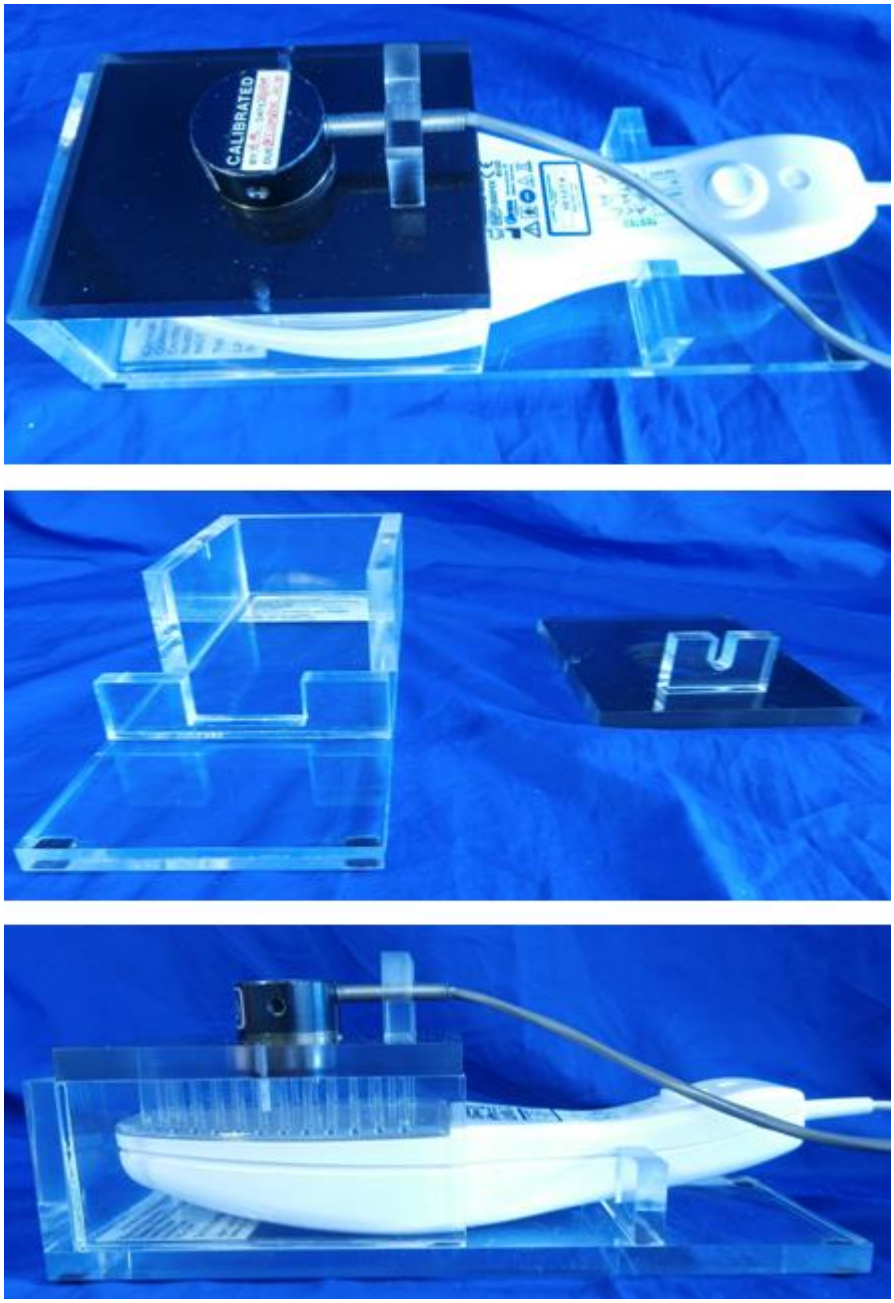

Figure 13 Photos showing three differing views of the test jig

7.3 Study 1: Photometric characterisation of the NB-UVB devices prior to their use in the trial

In order to achieve objectives 1,2 and 4, we developed the following protocol to test the photometric characteristics [spectral output, actual irradiance, consistency of irradiance during warm-up, longer-term stability of the irradiance-time curve] of the device with the LightTech tubes:

a. Measure the spectral output for 10 tubes and compare with the manufacturer's specification using the Bentham monochromator.

This test was to ensure that the tube emission spectrum was both as expected and consistent across tubes (Objective 1).

b. Measure the irradiance at 2 minutes following 'switch on' [to compare with manufacturer's specification] and integrated dose at various time points [from 15s to 210s in 15s intervals], to calculate average dose-rate as a function of time for each LightTech tube, then calculate the mean values and variance across all LightTech tubes.

We carried out these tests both to ensure that the tubes met the stated manufacturer's output at 2 minutes and also to investigate the irradiance changes during tube warm-up when the irradiance initially rises fairly rapidly, before dropping off more slowly. These tests evaluated whether the tube outputs were repeatable, thus allowing more confidence in any set treatment protocol (Objectives 1,2,4).

c. Measure irradiance to simulate various treatment regimen simulations [2 x 30% total; 2 x 65% total; 2 x 100% total] following the skin type VI treatment protocol [longest treatment times] for three lesions, simulating actual usage.

We carried out these tests to investigate whether the irradiance-time curve shape remained constant irrespective of usage. (Objectives 1,2,4)

d. Measure integrated dose for 50% total, 2 x 50% total, 100% total in single exposures. The 100% single exposure was conducted on two LightTech tubes.

We carried out this test to investigate if 'fractionation' of total exposure changed tube characteristics (Objectives 2,4).

Tests a and b were designed to test the absolute characteristics of the tubes and to assess the variability of performance. This helped us to develop cut-off tolerances for irradiance and integrated exposure when testing trial devices prior to issue to participants, excluding devices whose characteristics fell outside these tolerances.

Tests c and d were designed to test the fall-off in irradiance and integrated dose, to ascertain if any pre-burn was required and to inform the trial treatment protocols. It also gave an insight into whether or not tests done on used devices following participant use could be used to determine treatment protocol adherence by the trial participants.

7.4 Study 2: Quality assurance of devices prior to distribution to trial participants

Study 2 addressed Objective 3, ensuring consistency of performance for devices issued in the trial. For reasons of efficiency, devices were tested in batches of approximately 15-25 prior to release to participants. The tests undertaken included:

- A spectral irradiance test to look for any gross fault or set-up error in the supplied device [such as an incorrect tube fitted]
- Peak irradiance [3 minutes after start-up for all devices] to check if the device irradiance was within 20% of our validated irradiance values

Due to the large variability in tube irradiance at the manufacturer's specified time of 2 minutes post start-up, we measured irradiance at 3 minutes post-start-up, as we discovered that this was a more stable measure of individual tube performance (see results).

7.5 Results

Study 1 – Characterisation of Devices

Ten tubes from the same manufacturing batch were tested for spectral irradiance. The results of these measurements are shown in Figure 3. The results show almost exact coincidence of the spectral irradiance for all ten tubes. They also show good coincidence with the manufacturer's specified spectral irradiance. The main irradiance was at 313 nm, with subsidiary peaks at 365nm, 405nm and 435nm. There was a very small UVA component [365nm].

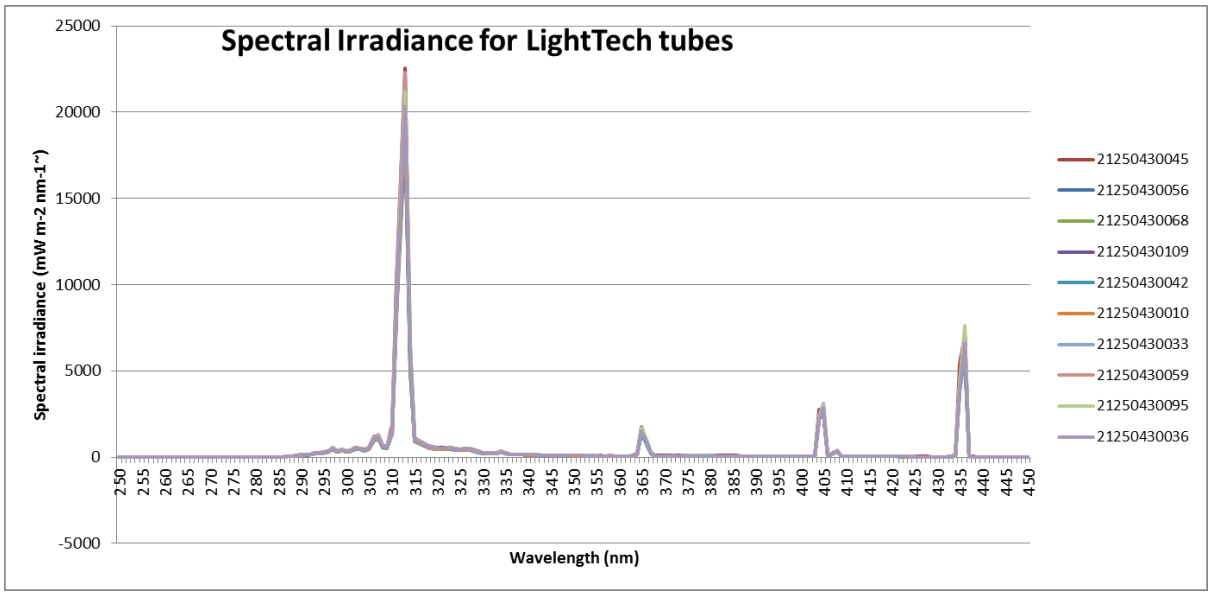

Figure 14 Spectral irradiance for the first batch of 10 tubes

Table 32 shows the irradiance results from the sample of ten tubes. These results are to be compared with the manufacturer's specification ['typical irradiance at 120s'] at the tube's mid-point

at the comb tip of 7 mWcm^{-2}. These results showed that most tubes would fall within our acceptance criteria of an output +/- 20% from the value used to inform the clinical treatment protocol.

Table 32 Summary statistics for the characterisation of the irradiance

Mean irradiance, mWcm^{-2}	Min irradiance, mWcm^{-2}	Max irradiance, mWcm^{-2}	Std. Dev. mWcm^{-2}	Manufacturer's Specified irradiance mWcm-2
4.02	3.58	4.50	0.26	7

[Summary statistics for the characterisation of the irradiance measured at the comb tip midway along the tube at 120s post-start-up, for the initial sample of ten LightTech tubes [cf. Manufacturer's specified irradiation at same time point, 7 mWcm^{-2}]

The mean device output was only 53% of the manufacturer's specified output. For clinical protocol derivation a mean tube irradiance of 4 mWcm^{-2} was used.

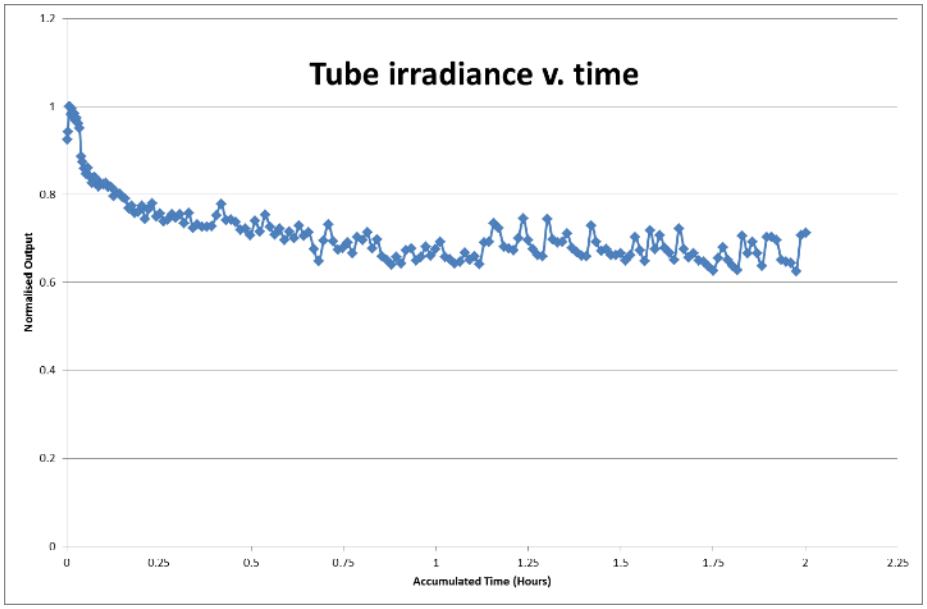

Figure 15 Tube irradiance (normalised to the maximum irradiance) as a function of time

The results of simulating various participant protocols on the irradiance are shown in Table 33.

Table 33 Average irradiances following simulated treatment regimens for type VI skin.

Treatment time [% of total fractions from the start]	Average % Drop (from mean start maximum value)
30%	23% [n=5]
65%	31% [n=4]
100%	37% [n=2]

The values in parentheses in column 2 are the number of tubes that contributed to the average.

The table shows the average irradiance and percentage drop from the initial maximum average irradiance at various time points during the treatment protocol for skin type VI for three lesions (the maximum number of lesions to be assessed in the trial). It allows for the repeated turning on and off of the device on different days and therefore includes multiple warm-up times, as would be the case for a real participant treatment regimen.

Study 2 – Results of devices prior to issue to participants

Although the spectral irradiance test in Study 2 was designed to ensure no devices with gross set-up errors (e.g. incorrect tube wavelength) were issued to participants, it also allowed us to track changes in tube manufacturing. The peak irradiance wavelength was noted to change from 313nm to 314nm after about a fifth of the batch processing. This slight change in the wavelength of the peak irradiance was not due to any calibration drift of our monochromator and was most likely due to changes in the phosphor composition of the fluorescent tubes. This change did not produce any significant change in the amount of UVA radiation.

Twenty-one batches were tested and 9/21 (43%) batches had devices where one or more devices showed an irradiance outside the range 3.22 – 4.82 $mWcm^{-2}$ (mean value +/- 20%). A total of 54 live devices were rejected out of a total tested of 425 (13%). One batch (24 live devices) was tested where all devices lay outside the required range. After confirming that this was not due to faulty bulbs, combs or voltage supply, it was assumed that a power supply fault was responsible and the devices were returned to the manufacturer. The batch sizes ranged from 15 to 25 units.

7.6 Discussion

The results of the characterisation tests on the LightTech tubes clearly showed a real output much lower than supplier information. This difference [a factor of approximately 0.6] would have required

an increase in treatment time of 75% to allow for the drop in output performance of the real-world tubes. These results show the importance of thoroughly characterising NB-UVB devices prior to use to ensure adequate treatment. Although the much lower output of the units could have potentially led to a reduction in efficacy, we accounted for the lower output by adjusting the treatment schedule used in the trial. Based upon our measurements, there is a need for cost-effective, higher irradiance tubes that can be used in such devices.

The tube irradiance as a function of time (Figure 15) was broadly the same for all tubes tested. For all tubes there was a brief (within first 2 minutes) increase in output, followed by a decrease in output characterised by a reducing gradient with a plateau reached after about 50% of the treatment time. To pre-burn the tubes to enable a constant output would therefore have required a pre-burn time of many hours. This could have been done in the setting of a research study but would be costly and potentially impractical when using the devices in clinical practice. One alternative approach would be to adjust the treatment schedule in the early stages of treatment, making allowances for the gradual loss of output. However, this would have been complicated to calculate and would not have allowed us to use a simple treatment schedule with fixed increments between treatments. We also felt that asking participants to recalculate doses themselves would add further complexity to the treatment, which might have reduced adherence. Moreover, any gradual loss of output in the early life of a unit will simply require that it is used for slightly longer periods with each subsequent use in order to achieve the expected mild degree of skin erythema and subsequent therapeutic response, and this would be achieved by simply moving on to the next step of the dosing schedule. Therefore, as the trial was pragmatic, reflective of real-life clinical practice, we decided not to pre-burn the tubes but instead to use them from new and to ask participants to follow the planned treatment schedule that included a two-minute ‘stabilisation’ period for the device prior to commencing treatment.

The fact that 1 in 8 devices were rejected due to their output lying outside the +/-20% cut-off point shows the importance of testing the devices prior to use. This quality control reduced the variance in treatment exposure amongst trial participants attributable to device output. It also demonstrates the need to check the output of devices before they are used in clinical practice as part of quality assurance, as is current practice for clinic-based treatment units.

Furthermore, as these devices may be purchased by members of the public, the output variation from specification and output variation between tubes shows the need for clinical supervision, backed up by robust quality assurance, during their use. Given these results we would recommend

any member of the public purchasing such a device directly from a supplier seek specialist dermatological advice before use.

The device tests described in this paper require expensive ultraviolet test equipment and scientific and technical expertise to interpret the results. These staff and equipment are not available at all hospitals and so may support the development of specialist centres of expertise supporting many dermatology services [a hub and spoke model].

We hope that our findings regarding the dosimetry and performance of hand-held NB-UVB units will help to inform the design of community-based phototherapy services in the future. There are, however, some additional considerations regarding the external validity of the work. In the trial, each device was used by only one participant. In a clinical service each device is likely to be used by several patients in succession, so the clinical service would have to decide whether to reissue the unit with the same bulb or, whether it would be better to fit a new bulb prior to the unit being re-issued. For the tubes used in this study the manufacturer states a useful tube life of 400 hours, which is far longer than the integrated treatment time for three lesions on a participant with skin type VI for 9 months, so a single tube could potentially be used for multiple patients, although protocols would have to be developed to ensure that devices were fit-for-purpose when re-issued.

As the study team required detailed technical specifications of the devices and tubes, a close working relationship with the supplier was essential in order to access such information; we received good support from the manufacturer in this respect. This would also be an essential requirement in the future when setting up a home-based phototherapy service using the devices.

Chapter 8: Discussion and conclusion

8.1 Main Findings

The HI-Light Vitiligo trial was a large, pragmatic RCT of home interventions (potent TCS and NB-UVB light therapy) for people with active and limited vitiligo. The combination of hand-held NB-UVB plus potent TCS for 9 months was found to be superior to potent TCS used on their own, was well tolerated and was potentially cost-effective (£2,329 unadjusted or adjusted £1,932 per additional treatment success, though there is currently no evidence to indicate how much a decision maker would be willing to pay for an additional treatment success). NB-UVB used as monotherapy was not superior to potent TCS and had a higher incremental cost per additional successful treatment than combination treatment compared to TCS alone.

Blinded evaluation of treatment success as assessed by a panel of three people with vitiligo supported the primary outcome, although treatment effects were larger and both NB-UVB and combination treatment were significantly better than TCS alone. It is unclear why blinded observers would value the treatments more than the participants in the trial, but it is possible that the trial participants balanced the observed treatment effects against the burden of adhering to treatment over 9 months.

Results for investigator-assessed percentage repigmentation, using digital images of the vitiligo, were also consistent with the participant-reported primary outcome (VNS). Percentage repigmentation is the most commonly used outcome in vitiligo trials[33], and so these results provide a useful context for comparison with other studies.

Quality of life was high for all groups at baseline and no differences were observed between groups following treatment.

Both NB-UVB and potent TCS were well tolerated. Erythema (grade 3 or 4) was a relatively common side-effect, but these episodes were limited to the small areas being treated and were managed effectively. The incidence of clinical skin thinning was rare despite the relatively long-term intermittent use of potent TCS, including on the face.

Sensitivity analyses were supportive of the main findings and participants who adhered to the treatment regimen by ≥ 75% were more likely to achieve treatment success. There was no difference between the treatment groups according to age (adults versus children) or duration of vitiligo (≥4 years versus < 4 years).

In line with clinical experience, vitiligo patches on the hands and feet responded less well to treatment; this was true for whatever interventions were being used.

At 3 months, over 90% of participants in all three groups showed onset of treatment response at the target patch, suggesting that all were effective in stopping the spread of vitiligo. However, onset of treatment response was defined as “stopped spreading (“stayed the same” or “improved”), which could have resulted in an over-estimation of treatment effect if potential participants over reported recent changes to the target patch in order to gain access to treatment.

Interpretation of results for ‘maintenance of treatment response’ were limited by low follow-up rates at 12 to 21 months. Nevertheless, the results suggest that treatment response may be lost quite rapidly once interventions are stopped and that maintenance therapy may be required to retain the pigmentation gained during treatment.

Process evaluation findings suggested that patients and healthcare professionals were positive about the role of combination treatment in the management of vitiligo.

Despite being time consuming and (potentially) complex, both participants and healthcare professionals indicated that, with appropriate support, combination treatment could be managed at home. Appropriate training and on-going monitoring, particularly in the early stages of treatment are essential, especially given concerns about potential side effects.

People with vitiligo were perceived to have few treatment options, thus supporting the broader use of combination treatment in the NHS, with some caveats about which patients might benefit most. Those with a lifestyle that is incompatible with regular time-consuming treatments, unrealistic expectations of treatment, or poor levels of adherence to prior treatments may be poor candidates for combination treatment.

Both healthcare professionals and commissioners recognised that the need for a developed infrastructure (including nursing support and medical physics provision) might be a barrier to broader NHS provision. Regional clinics might be a possible solution, as might some form of mixed economy approach, where patients purchase light-therapy devices alongside NHS support and training.

Relevance to the wider literature

These results show that combination treatment with NB-UVB and potent TCS is more effective than a single intervention (in this case, TCS). This is consistent with previous research, which has shown that combination treatments are generally more effective than monotherapies in treating vitiligo, although overall response rates, both in our study and previous research, are generally modest.[22, 25, 26]

Although there have not been any studies assessing the same interventions as those used in this study, the response rates are comparable with other studies. A meta-analysis of studies assessing phototherapy for vitiligo[78], including 29 prospective studies of NB-UVB, reported a 'marked response' (>75% repigmentation) in around 19% of participants after 6 months of NB-UVB monotherapy. This is similar to the rates of treatment success in our study, measured using the VNS (18% for NB-UVB only and 28% for combination at 6 months), although we observed lower success rates based on ≥75% repigmentation (5% for NB-UVB only and 11% for combination at 6 months). The same meta-analysis reported better response rates for vitiligo on the head and neck, which is consistent with our study[78].

No other studies have compared the specific combination of NB-UVB and mometasone furoate with mometasone alone, so direct comparison is difficult. One study comparing the combination of NB-UVB and clobetasol propionate (a more potent TCS) with NB-UVB alone[79] was identified in the Cochrane systematic review of interventions for vitiligo[22]. This study suggested that combination treatment might be more effective than NB-UVB monotherapy, but the study was small and so lacked power to demonstrate any statistically significant difference between the intervention groups; the relative risk ratio for achieving >75% repigmentation was 1.38 (95% CI 0.71-2.68)[79].

No significant safety issues have been identified in previous small studies of home-based hand-held phototherapy devices for vitiligo, used instead of hospital NB-UVB therapy[25, 26], and this is confirmed by the findings of our study. Long-term NB-UVB treatment (mean number of treatments = 211) in a study of patients with darker skin types conferred no increase in skin cancer risk, suggesting that NB-UVB can safely be continued for longer periods than in our study, although most patients in that study were skin types IV-VI[80]. Large cohort studies of patients having long-term treatment with NB-UVB have also shown no significant increase risk in skin cancer risk from this treatment[39, 40].

Although combining NB-UVB and calcineurin inhibitors (e.g. tacrolimus) was discouraged in the past, due to concerns over a possible increased risk of skin cancer, a number of studies assessing this combination of treatment have been published over the last few years. A systematic review by Arora

et al[81] identified three studies comparing a combination of NB-UVB and tacrolimus with NB-UVB monotherapy. Meta-analysis of two of these studies showed combination treatment to be more effective than NB-UVB monotherapy in achieving >75% repigmentation, although only just (RR 1.34; 95% CI 01.05–1.71). It is possible that further studies comparing these interventions will provide sufficient data to make the confidence estimates stronger, but this remains to be seen.

Strengths and Limitations

This was a large, pragmatic trial that was designed and managed in collaboration with an accredited clinical trials unit. Using a patient-reported primary outcome meant that treatment success reflected the views of people with vitiligo and was supported by blinded outcome assessment using digital images for both VNS and percentage repigmentation; both of which have been recommended for inclusion in vitiligo clinical trials by people with vitiligo.[35]

As found in other vitiligo trials[22], retention throughout the trial was challenging. Just over 70% of participants provided primary outcome data at 9 months, and fewer than 50% provided data by 21 months. This limited interpretation of some of the results, especially during the long-term follow-up phase.

Since loss to follow-up was higher than originally anticipated, the trial lacked power to provide a high level of precision around the point estimates.

Adherence to treatment regimens was quite low (see Table 6). This was most likely due to the time burden of treatments, particularly the active or dummy NB-UVB devices. This is a limitation of the study but this was a pragmatic trial and treatments were delivered by the participant and / or their carers at home (with nursing support). It is possible that participants adhered more to trial interventions as a result of being in a trial, and this may have led to an overestimate of treatment effects. However, we think that overall, the level of use of the treatments is reflective of how they would be used in real life.

We used a single, standardised treatment schedule, which we asked all participants to follow. This started at a very low dose and then built up to higher doses in small increments. This will have meant that for participants with darker skin types, the first few doses will have been lower than those used in conventional hospital-based phototherapy, where starting doses are determined by measuring the Minimum Erythemal Dose (MED) prior to starting treatment. However, participants would all move up the schedule to longer treatment times, and over the course of treatment (up to nine months), these smaller initial doses are not likely to have had a significant impact on the total NB-UVB dose received by those participants using active devices.

Participants were encouraged to choose a target patch that was genuinely the one in which they most wanted to see a difference. If they had two patches on different parts of the body which they were equally keen to see an improvement in, and if one of the patches was on the hands and feet, they were advised that the response may not be as good on the hands and feet, but they could still choose for the hand / foot patch to be their target patch. Many participants still chose a hand / foot patch as their target patch, but it is possible that some participants may have decided to change the target patch to one on the head and neck or rest of body. This could have introduced bias into the study findings. However, this is similar to the situation in clinical practice, where a patient may be advised that treatment of vitiligo in certain anatomical locations may be less effective, and that it may make more sense to concentrate on treating areas of vitiligo that are more likely to responds to treatment.

Generalisability

This trial has good external validity as it was a large, pragmatic trial with few exclusions, although all participants were required to have active vitiligo that affected less than 10% of their body surface area. People with more extensive vitiligo are unlikely to find these interventions helpful as the treatments would become overly burdensome.

The trial included both children and adults and treated different body sites. Planned sub-group analyses explored the impact of these characteristics but found no evidence of differential treatment response by age or body site, other than the overall poorer response rates on the hands and feet. People with all skin types and ethnicities were included in the trial as this reflected the types of patients typically presenting for vitiligo treatment within the UK NHS. We did not exclude participants with lighter skin types (Types I and II), as vitiligo can cause considerable distress in such people as well as those with darker skin types[16, 82]. A post-hoc analysis by skin type found no differential treatment response in people with paler skin types (types I to III) or those with darker skin types (types IV to VI), although we would emphasise that this was an exploratory, post-hoc analysis and the study was not specifically powered for this analysis.

The trial was designed to reflect normal clinical practice as far as possible. Hand-held NB-UVB devices such as those tested in this study are not widely available within the UK National Health Service at present, although a few sites do offer treatment with similar devices and they can also be purchased online and used at the user's own risk. In the trial, nurses in secondary care dermatology departments delivered training on use of the treatments, and participants were reviewed every 3 months during clinic visits. Additional support was provided by telephone as required, if participants had queries about use of the interventions or experienced side effects.

The process evaluation conducted alongside this study identified the importance of the support provided to participants, in order to enable them to use the treatments safely. Participants and investigators agreed that the complexity of the treatments meant that support and close monitoring were essential. Some participants had considered purchasing a light therapy device, but had decided against this due to a lack of the necessary support infrastructure. If the treatments were introduced into the NHS, the cost of providing this support infrastructure would need to be taken into account, and healthcare decision makers would have to decide how much they are willing to pay to achieve a successful treatment. The relative lack of other treatment options, and the likely high cost of newer drug treatments currently being developed, wounblinduld be important to consider when making such decisions.

8.2 Conclusions

Implications for healthcare

The HI-Light Vitiligo Trial demonstrates that combination treatment with NB-UVB and potent TCS is superior to potent TCS alone, although the benefits are likely to be modest. Combination treatment was safe, well tolerated and cost-effective for people with limited vitiligo that had been active within the last 12 months. Given uncertainty about how much decision makers would be willing to pay to achieve an additional treatment success (as defined in this study) it is unclear whether combination treatment is cost-effective.

Patients starting vitiligo treatments should be made aware of the considerable time commitment required, and the likely duration of treatment over many months. Clinical review at 3 months appears to be an appropriate time point at which to judge whether further treatment is likely to be beneficial.

Our study confirmed that vitiligo on the hands and feet responds less well to treatment, so treating these anatomical areas may be difficult to justify when resources are limited.

Hand-held, home NB-UVB therapy appears to be a useful treatment option for people with vitiligo and provides considerable advantages over hospital NB-UVB therapy (which requires hospital visits 2-3 times per week). Home NB-UVB requires training and support from healthcare professionals with experience of delivering phototherapy services and is time intensive for patients.

Use of mometasone furoate 0.1% ointment (a potent corticosteroid) as first-line treatment for vitiligo is supported, as it achieved treatment success in 1 in 6 individuals and was effective in stopping the spread of active vitiligo patches. Stopping the spread of vitiligo is an important

treatment outcome to people with the condition [21, 33]. These trial results suggest that potent TCS is safe in both adults and children when used one week on, one week off for 9 months.

Treatment effects were lost once interventions were stopped, suggesting that maintenance therapy is likely to be needed to prevent further loss of pigment.

Compared to potent TCS, combination treatment had a lower incremental cost effectiveness ratio than NB-UVB monotherapy (meaning that an additional treatment success can be attained for a lower cost), although the mechanism for widespread implementation of a home-based NB-UVB service for skin disorders within the NHS has yet to be established.

Qualitative findings from our mixed methods process evaluation study suggested that people with vitiligo and healthcare professionals who treat them would value the provision of home NB-UVB as a useful treatment option for the management of vitiligo, despite the relatively modest treatment effects. Both trial participants and healthcare professional suggested that some form of 'mixed economy' might be most effective way of providing home light therapy. This could potentially involve patients leasing or purchasing a phototherapy device, and the NHS providing the necessary training, quality assurance and support for patients. This would reduce the likely cost to the NHS (see sensitivity analysis in section 4.13) but would have equity implications in that treatment would only be accessible to those patients able to afford it.

These findings need to be disseminated to a wide audience. People seeking treatment for vitiligo are unlikely to receive any treatment if they do not receive appropriate advice from health professionals. In the UK, people with vitiligo are likely to consult a GP initially, and research amongst members of the Vitiligo Society suggest people view their GP as their primary source of information, although GPs appear to have low awareness of vitiligo.[83] The NICE CKS guideline suggests that people seeking treatment for vitiligo may be prescribed TCSs and/or referred to dermatology[84]. However, anecdotally, such management does not always seem to be followed. The safety data from this trial suggest that GPs can be reassured that adverse effects are rare if potent TCSs are used long-term once daily on alternate weeks (one week on, one week off).

Implications for research

Participants in the HI-Light Trial reported relatively high quality of life scores at baseline using both generic and vitiligo-specific quality of life instruments. Despite having good quality of life, all participants were keen to access vitiligo treatments and were wiling to use them over many months, suggesting that something other than quality of life was motivating treatment choices. It is not clear whether this was because the trial focussed on people with limited vitiligo (which had limited impact

on their quality of life), or whether the quality of life instruments themselves were insufficiently sensitive to detect the impact of vitiligo, particularly in relation to psychological impact of the condition.

Since home-based phototherapy services for the management of skin disorders are currently available in only a small number of specialist centres, further research is required to establish the best ways of implementing a home-based light therapy service across the UK. This might usefully involve a hub-and-spoke model whereby specialist medical physics units perform the testing and maintenance of devices for a number of departments.

We used participant-reported treatment success as the primary outcome, based on the noticeability of the vitiligo (VNS), to ensure that vitiligo treatments were judged against criteria that are meaningful to people with vitiligo. Further work is required to establish the validity, responsiveness and interpretability of the VNS. In particular, it would be helpful to establish how patients value a 'partial treatment' response as measured by the VNS.

The HI-Light Vitiligo Trial was designed to address two of the questions prioritised by healthcare professionals and people with vitiligo in the James Lind Alliance Vitiligo Priority Setting Partnership[21]. Many of the Top 10 priorities remain unanswered (**Box 1).**

James Lind Alliance Vitiligo Priority Setting Partnership top 10[21]

1. How effective are systemic immunosuppressants in treating vitiligo?

2. How much do psychological interventions help people with vitiligo?

3. Which treatment is more effective for vitiligo: light therapy or calcineurin inhibitors (e.g. tacrolimus, pimecrolimus)?

4. How effective is UVB light therapy when combined with creams or ointments in treating vitiligo?

5. What role might gene therapy play in the treatment of vitiligo?

6. How effective are hormones or hormone related substances that stimulate pigment cells (MSH analogues, afamelanotide) in treating vitiligo?

7. Which treatment is more effective for vitiligo: calcineurin inhibitors or steroid creams/ointments?

8. Which treatment is more effective for vitiligo: steroid creams/ointments or light therapy?

9. How effective is the addition of psychological interventions to patients using cosmetic camouflage for improving their quality of life?

10. How effective is pseudocatalase cream (combined with brief exposure to UVB light) in treating vitiligo?

In addition, two treatment uncertainties were suggested as "ones to watch", as these interventions were still in an early investigative stage.

1. How effective is piperine (black pepper) cream in treating vitiligo?

2. What role might stem cell therapy play in treating vitiligo?

Box 2 James Lind Alliance Vitiligo Priority Setting Partnership Top Research Priorities

Future research priorities that have emerged from the HI-Light Vitiligo Trial include the need for:

1. Development and testing of new vitiligo treatments with a greater response and longer-lasting effects.
2. Investigation of treatments suitable for people with widespread vitiligo.
3. Research into different strategies to maintain treatment response once treatments are stopped
4. Further development and validation of outcome instruments to be included in the vitiligo core outcome set, to facilitate combining of trial results in meta-analyses.

Chapter 9: Acknowledgements

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Contributors to the HI-Light trial:

- Independent Trial Steering Committee: Khaled Ezzedine (Department of Dermatology, Paris-Est Créteil Val-de-Marne University), Chris Edwards (Consultant Medical Physicist, Department of Dermatology, St Woolos Hospital, Newport), Marco Singh (patient representative and Trustee and Treasurer, Vitiligo Society) and Ophelia Dadzie (Consultant Dermatologist, Hillingdon Hospital, Uxbridge).
- Data Monitoring Committee: Robert Dawe (Consultant Dermatologist, Dermatology Department, Ninewells Hospital, Dundee), Michelle Collinson (Senior Medical Statistician, University of Leeds), Robert Sarkany (Consultant Dermatologist, St John's Institute of Dermatology, London) and Bonnie Cundill (Principal Statistician, Complex Interventions Division Clinical Trials Research Unit, Leeds)
- Nottingham CTU: Daniel Simpkins and Chris Rumsey (management of the trial database systems); Jessica Haywood, Sarah Walker, Mathew Foster and Stella Tarr (data management); Alexandra Erven and Isobel Hawley (blinded control of light devices); Gill Bumphrey and Paula Blance (clinical trials pharmacy); Jenny Smithson and Hayley Gregory (monitoring activities); Melanie Boulter, Sharon Ellender and Hayley Foster (quality assurance).
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    - Birmingham Children's Hospital, Birmingham Children's Hospital NHS Foundation Trust (Gemma Baker, Jason Pitt, Lucy Cooper, Karen Doherty, Gemma Grovenor, Dharshini Sathish Kumar, Needa Mohamed, Katie Heffernan, Charlotte Cottrill (nee Lilley) and Melanie Rooney)
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9.1 Contribution of authors

Jonathan M Batchelor (Consultant Dermatologist, Chief Investigator) contributed to the conception and design of the study, trial oversight, interpretation of the data, and drafted and critically reviewed the report

Kim S Thomas (Professor of Applied Dermatology Research, lead applicant) contributed to the conception and design of the study, trial oversight, interpretation of the data, and drafted and critically reviewed the report

Perways Akram (Technical Services Manager, testing and calibration of NB-UVB devices) contributed to the design of the study, data collection and analysis, interpretation of the data, and drafted and critically reviewed the report

Jaskiran Azad (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Anthony Bewley (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Joanne R Chalmers (Senior Research Fellow, lead for process evaluation study) contributed to the conception and design of the study, data collection and analysis, interpretation of the data, and drafted and critically reviewed the report

Seau Tak Cheung (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Lelia Duley (Former Director of NCTU) contributed to the conception and design of the study, and critically reviewed the report

Viktoria Eleftheriadou (Dermatology Specialist Registrar) contributed to the conception and design of the study, data collection and critically reviewed the report

Rob Ellis (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Adam Ferguson (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Jon MR Goulding (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Rachel H Haines (Senior Trial Manager) contributed to the conception and design of the study, trial oversight, interpretation of the data, and critically reviewed the report

Hamdi Hamad (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

John R Ingram (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Bisola Laguda (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Paul Leighton (Associate Professor of Applied Health Services Research, qualitative research lead for process evaluation) contributed to the conception and design of the study, data collection and analysis, interpretation of the data, and drafted and critically reviewed the report.

Nick Levell (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Walter Machado (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Areti Makrygeorgou (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Garry D Meakin (Trial Manager) contributed to the design and delivery of the study, trial oversight, interpretation of the data, and drafted and critically reviewed the report

Adam Millington (Specialist Pharmacist, Trial Pharmacist) contributed to the design and delivery of the study, development and packaging of IMP, and critically reviewed the report

Malobi Ogboli (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Amirtha Rajasekaran (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Jane C Ravenscroft (Consultant Dermatologist, Principle Investigator) contributed to the conception and design of the study, trial oversight, data collection, interpretation of the data, and critically reviewed the report

Andy Rogers (Lead Interventional MPE, testing and calibration of NB-UVB devices) contributed to the conception and design of the study, trial oversight, data collection, interpretation of the data, and drafted and critically reviewed the report

Tracey H Sach (Professor of Health Economics, Senior Health Economist) contributed to the conception and design of the study, trial oversight, analysis and interpretation of the data, and drafted and critically reviewed the report

Miriam Santer (Associate Professor in Primary Care Research, general practitioner) contributed to the conception and design of the study, trial oversight, interpretation of the data, and critically reviewed the report

Julia Stainforth (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Wei Tan (Trial Statistician) contributed to the conception and design of the study, trial oversight, interpretation of the data, and drafted and critically reviewed the report

Shyamal Wahie (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Jen White (Trial Co-ordinator) contributed to delivery of the study, trial oversight, interpretation of the data, and critically reviewed the report

Maxine E Whitton (Patient Partner) contributed to the conception and design of the study, trial oversight, interpretation of the data, and critically reviewed the report

Hywel C Williams (Consultant Dermatologist) contributed to the conception and design of the study, interpretation of the data, and critically reviewed the report

Andrew Wright (Consultant Dermatologist, Principle Investigator) responsible for oversight at recruiting centre and critically reviewed the report

Alan A Montgomery (Director of NCTU, Senior Trial Statistician) contributed to the conception and design of the study, trial oversight, interpretation of the data, and drafted and critically reviewed the report

9.2 Publications

Home interventions and light therapy for the treatment of vitiligo (HI-Light Vitiligo Trial): study protocol for a randomised controlled trial. BMJ Open. 2018 Apr 3;8(4):e018649. doi: 10.1136/bmjopen-2017-018649.

Survey and online discussion groups to develop a patient-rated outcome measure on acceptability of treatment response in vitiligo. BMC Dermatol. 2014 Jun 14;14:10. doi: 10.1186/1471-5945-14-10.

Validation of the Vitiligo Noticeability Scale: a patient-reported outcome measure of vitiligo treatment success. Br J Dermatol. 2016 Feb;174(2):386-94. doi: 10.1111/bjd.14208. Epub 2015 Dec 14.

9.3 Data Sharing

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Appendix 1 Addendum to HI-Light Statistical Analysis Plan (SAP) Final Version 1.0 dated 15 October 2018

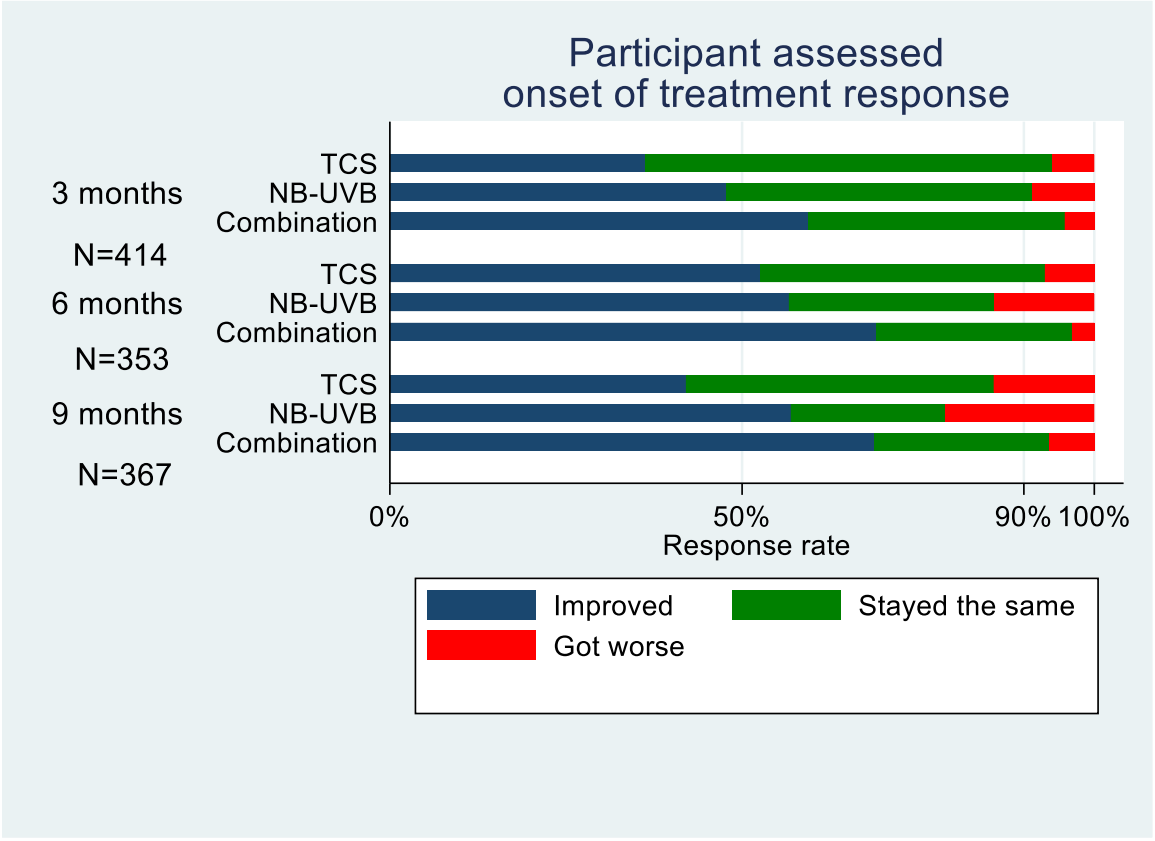
Changes from protocol v5.0 Additional points of clarification are outlined below. These amendments provide additional information on how the outcomes were reported and analysed, but do not substantially change the outcomes as defined prior to database lock.

Protocol	SAP	Justification
Digital image assessment of the target patch at 9 months by independent assessors is described as a secondary analysis of the primary outcome.	The digital image assessment of the target patch at 9 months by independent assessors will be reported as an additional secondary outcome.	More appropriate as a secondary outcome as based on new data from a different source to the primary outcome.
Maintenance of treatment response will be reported for each of the three body regions.	Maintenance of treatment response will be reported for the target patch only.	Due to lower than expected follow-up rates, there is insufficient data to present the maintenance of treatment response at 12, 15, 18 and 21 months for each body region.
Patient reported treatment success by body region will be assessed at 3, 6 and 9 months.	Patient reported treatment success by body region will be assessed at 9 months only. Treatment success at 3 and 6 months will be presented descriptively.	Minimise risk of type I errors from multiple hypothesis testing
Percentage repigmentation will be assessed at 3, 6 and 9 months.	Percentage repigmentation will be assessed using digital image assessment by a blinded clinical assessor at 9 months. Where available, data from nurse assessments at 9 months will be used for missing blinded assessor data. Assessments carried out by nurses at 3 and 6 months will be presented descriptively.	Minimise risk of type I errors from multiple hypothesis testing
Participant-reported treatment burden will be presented at 3, 6 and 9 months based on average duration and number of treatment sessions and adherence with the treatment schedule. To be presented for light therapy and topical corticosteroid therapy separately.	Treatment burden will focus on the burden of light therapy and will be presented alongside adherence data as a process measure. Average session duration for those who received an active light device will be reported at 3, 6 and 9 months and the proportion of participants who reported difficulties with treatment (including time burden) with be presented over 9 months. For TCS, average time per session will not be reported as the time required for this was felt to be minimal. However, treatment burden for those receiving active TCS will be presented for those who reported experiencing difficulties with treatment (including time burden) presented over 9 months. .	Calculating the duration of light treatment based on placebo devices is not appropriate as the dosing schedule would always increase as no erythema will have been experienced during the dosing schedule, and so treatment times are likely to be longer. Data regarding the duration of treatment sessions was not collected for TCS treatment as the time required to apply ointment is minimal.

Appendix 2 Participant reported VNS treatment success at all assessed patches at 3 and 6 months

	TCS	NB-UVB	Combination
Treatment success for head and neck			
At 3 months	13/73(18%)	15/71(21%)	19/73(26%)
At 6 months	15/62(24%)	15/57(26%)	29/68(43%)
Treatment success for hands and feet			
At 3 months	7/94(7%)	10/89(11%)	2/87(2%)
At 6 months	10/81(12%)	11/73(15%)	10/74(14%)
Treatment success for rest of body			
At 3 months	7/106(7%)	8/99(8%)	11/104(11%)
At 6 months	11/91(12%)	13/86(15%)	25/91(27%)

Appendix 3 Participant assessed onset of treatment response



Appendix 4 Target patch % repigmentation assessed by nurse at 3, 6, and 9 months

		TCS	NB-UVB	Combination
Repigmentation of target patch at 3 months				
	0-24%	119(89%)	110(81%)	111(78%)
	25-49%	7(5%)	13(10%)	15(10%)
	50-74%	4(3%)	7(5%)	11(8%)
	75-100%	4(3%)	6(4%)	6(4%)
Repigmentation of target patch at 6 months				
	0-24%	91(79%)	73(65%)	75(60%)
	25-49%	6(5%)	24(21%)	17(14%)
	50-74%	10(9%)	10(9%)	19(15%)
	75-100%	8(7%)	6(5%)	14(11%)
Repigmentation of target patch at 9 months				
	0-24%	83(72%)	72(63%)	66(55%)
	25-49%	16(14%)	14(12%)	18(15%)
	50-74%	6(5%)	18(16%)	14(12%)
	75-100%	10(9%)	11(10%)	21(18%)

Appendix 5 Summary of related AEs by preferred term name in MEDDRA coding

	TCS (n = 33)	NB-UVB (n = 69)	Combination (n = 104)	Total (n=206)
Acne	0	1	2	3
Application site pruritus	0	2	0	2
Blister	0	4	2	6
Contusion	1	0	2	3
Dry skin	3	0	5	8
Erythema	3	29	45	77
Folliculitis	0	0	1	1
Haemangioma	0	1	0	1
Hair growth abnormal	5	2	4	11
Herpes virus infection	0	2	0	2
Herpes zoster	0	0	1	1
Koebner phenomenon	0	1	0	1
Lip dry	0	0	1	1
Lip pain	0	0	1	1
Melanocytic naevus	0	1	0	1
Miliaria	0	0	2	2
Night sweats	0	1	0	1
Oral discomfort	0	0	1	1
Oral herpes	1	4	6	11
Pain in extremity	0	0	1	1
Pain in jaw	1	0	0	1
Pain of skin	1	0	0	1
Paraesthesia	0	0	1	1
Polymorphic light eruption	0	1	0	1
Pruritus	3	7	10	20
Pustular psoriasis	0	0	1	1
Rash	6	3	4	13
Rash pruritic	1	2	6	9
Rhinalgia	1	0	0	1
Skin atrophy	5	1	1	7
Skin depigmentation	1	0	0	1
Skin exfoliation	0	5	0	5
Skin hyperpigmentation	0	0	2	2
Skin papilloma	0	0	1	1
Skin striae	1	0	0	1
Spider vein	0	1	3	4
Telangiectasia	0	0	1	1
Vitiligo	0	1	0	1

Appendix 6 Utility and QALYs for participants aged 11 and over (available case data, Secondary Cost utility analysis)

	NB-UVB only (n=148)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Devlin et al 2018 utility value					
Secondary outcomes					
EQ-5D-5L Baseline	0.9300	0.1346 (139)	0.9456	0.0805 (151)	-0.0156 (-0.0410 to 0.0098)
EQ-5D-5L 9 months	0.9527	0.1108 (89)	0.9231	0.1240 (97)	0.0295 (-0.0046 to 0.0637)
QALYs at 9 months	0.7082	0.0699 (89)	0.6989	0.0694 (97)	0.0093 (-0.0109 to 0.0295)
	Combined (n=153)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Secondary outcomes					
EQ-5D-5L Baseline	0.9247	0.1381 (147)	0.9456	0.0805 (151)	-0.0209 (-0.0466 to 0.0048)
EQ-5D-5L 9 months	0.9446	0.1057 (97)	0.9231	0.1240 (97)	0.0215 (-0.0111 to 0.0540)
QALYs at 9 months	0.7064	0.0757 (96)	0.6989	0.0694 (97)	0.0075 (-0.0131 to 0.0282)
	NB-UVB only (n=148)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
OHE 2018 utility value set					
Secondary outcomes					
EQ-5D-5L Baseline	0.9299	0.1374 (139)	0.9461	0.0800 (151)	-0.0162 (-0.0420 to 0.0095)
EQ-5D-5L 9 months	0.9537	0.1101 (89)	0.9239	0.1245 (97)	0.0298 (-0.0044 to 0.0639)
QALYs at 9 months	0.7086	0.0696 (89)	0.6996	0.0690 (97)	0.0090 (-0.0110 to 0.0291)
	Combined (n=153)		**TCS only (n=155)**		**Mean difference (95% CI)**
	Mean	**Std dev**	**Mean**	**Std dev**	
Secondary outcomes					
EQ-5D-5L Baseline	0.9250	0.1399 (147)	0.9461	0.0800 (151)	-0.0211 (-0.0470 to 0.0048)
EQ-5D-5L 9 months	0.9448	0.1059 (98)	0.9239	0.1245 (97)	-0.0209 (-0.0118 to 0.0535)
QALYs at 9 months	0.7068	0.0754 (96)	0.6996	0.0690 (97)	0.0073 (-0.0132 to 0.0278)

Appendix 7 Survey of recruiting centre staff

Introductory page:

In anticipation of the Hi Light Trial Results day we would like to ask you some questions about your experience of providing hand-held phototherapy to the Hi Light participants.

We are particularly interested to hear about any insight that you would like to share with those that might be thinking about providing a similar therapy to their patients.

Context to these questions:

Existing evidence points to the benefits of phototherapy (in combination with other treatments) in the management of vitiligo; existing evidence points to the potential for home-based phototherapy using hand-held devices.

Some consideration of the clinical aspects of this (dosing, etc.) is manifest in the literature, but little has been said about service organisation and how best to delivery this type of therapy.

The NHS is a distinct context for delivering this type of service.

About you:

Are you: a doctor / a nurse / a specialist dermatology nurse / other(?)

Prior to Hi Light had you been involved in any form of phototherapy service? Y/N

What was your role in the Hi Light trial?

Are you already aware of the Hi Light trial results? Y/N

<u>Question 1:</u>

Do you agree that home-based phototherapy should be made more widely available for vitiligo patients?

strongly agree / agree / neutral / disagree / strongly disagree

We appreciate that the Hi Light results will ultimately inform this decision, but at this point we would welcome your intuitive response.

Can you explain your response? What is it about home-based phototherapy (and your experiences as part of Hi Light) that encourages, or discourages, you about its use?

Free-text response box….

<u>Question 2:</u>

Do you think that home-based phototherapy is appropriate for all vitiligo patients?

All patients / most patients / some patients / few patients / no patients

Could you explain your answer? What factors might influence whether a patient is appropriate for home-based phototherapy?

We would be interested to hear if you think that there are types of vitiligo presentation which are more, or less, appropriate for home-based phototherapy.

We would also be interested to hear if you think that lifestyle /personality/ personal circumstance are important in this decision.

Free-text response box….

Question 3:

Do you agree that delivering a home-based phototherapy service is feasible in the NHS?

strongly agree / agree / neutral / disagree / strongly disagree

We appreciate that ultimately this is a decision that commissioners will make, but we would invite your comment about the practical challenges that this might involve.

What were the difficulties and challenges that you found in delivering the Hi Light trial? Do you have any suggestions that would make a home-based phototherapy service easier to deliver or manage?

Free-text response box….

Question 4:

Do you think that participants (and their families) found hand-held phototherapy easy to do at home?

Very easy / easy / neutral / difficult / very difficult

We would be interested to hear about any difficulties or challenges that participants experienced with the hand-held phototherapy (and/or steroid cream).

We would be interested to hear about any strategies or techniques that participants used to manage, and about the nature of support that you offered them in this.

Free-text response box….

Question 5:

How important do you think it is for any hand-held phototherapy devices to be provided and maintained by an NHS provider?

Can you explain why you think this?

Do you have any thoughts about patients purchasing their own hand-held phototherapy unit? Via the NHS? Via a commercial provider?

Free-text response box….

Question 6:

Do you have any other comments, or recommendations, that would help others to establish and run a home-based phototherapy service for vitiligo.

Do you have any top-tips that you would like to share?

Free-text response box….