Home Interventions and Light therapy for the treatment of vitiligo (Hi-Light vitiligo)

Statistical Analysis Plan

Final version 1.0
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Based on Protocol version 5.0 (dated 18 Jan 2018)
Trial registration ISRCTN17160087

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
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Abbreviations

Abbreviation	Description
ADR	Adverse Drug Reaction
ADE	Adverse Device Event
AE	Adverse Event
BNF	British National Formulary
CF	Consent Form
CHU 9D	Child Health Utility 9D
CI	Chief Investigator (overall)
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HTA	Health Technology Assessment
MED	Minimum Erythema Dose
MET	Maximum Exposure Time
MHRA	Medicines and Healthcare products Regulatory Agency
NB-UVB	Narrowband Ultraviolet B
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NIHR	National Institute of Health Research
PI	Principal Investigator (at a local centre)
PICS	Patient Identification Centres
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCS	Topical corticosteroid
TMG	Trial Management Group
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
UV	Ultraviolet
VitiQOL	Vitiligo-specific Quality-of-Life

Changes from protocol v5.0

Protocol	SAP	Justification
Protocol includes both participant assessed and investigator assessed onset of treatment response as secondary outcome.	The SAP is more focused on investigator assessed onset of treatment response.	Both assessments from participant and investigator will be described with a focus of interpretation on investigator assessed. As the latter is less biased.
The protocol states investigator-assessed onset of treatment response is for all assessed patches	Only assessment for the target patch is used in analyses	Further discussions among the trial team revealed that onset of treatment response can only be assessed on active patches. Target patch by definition is the one we are certain that it is active. We will however report onset of treatment response by body region descriptively.
The protocol does not currently have subgroup analysis according to hypomelanotic	A subgroup analysis is specified according to whether patch is hypomelanotic	This is true, but is was stated in the protocol that "Further secondary analyses of the primary outcome will be defined in the statistical analysis plan prior to locking the trial database." – we have chosen to explore the impact of whether or not the vitiligo was hypoomelanotic or not as it has been reported in the literature that this feature of the vitiligo is an indicator of how active the disease is at start of treatment and therefore might predict treatment response.

1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the NIHR Health Technology Assessment-funded Hi-Light (Home Interventions and Light therapy for the treatment of vitiligo) trial.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of *a priori* and *post hoc* analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis plan will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the analysis plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

2.1. Trial aims and objectives

The purpose of the trial is to provide information on the comparative effectiveness of (i) home-based NB-UVB (Narrowband ultraviolet B) light, and (ii) the combination of topical corticosteroids and home-based NB-UVB light therapy versus topical corticosteroids (mometasone furoate 0.1% ointment) for the management of early and limited vitiligo in adults and children.

2.1.1. Primary objective

To assess the comparative safety and effectiveness of:

- NB-UVB light compared to potent topical corticosteroid
- The combination of NB-UVB light plus topical corticosteroid, compared to topical corticosteroid alone

2.1.2. Secondary objectives

- To assess whether treatment response (if any) is maintained once the intervention is stopped.
- To compare the cost-effectiveness of the interventions.

2.2. Trial design and configuration

Multi-centre 3-arm, parallel group, placebo-controlled, double-blind, randomised trial, with a nested process evaluation study. Treatment will be for up to 9 months, with follow-up to assess maintenance of repigmentation for 12 months after end of treatment (21 months post-randomisation).

2.3. Trial centres

Participants were identified from secondary care, primary care and through local advertising. Randomisation took place in secondary care.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

1. Patients 5 years of age or over with a diagnosis of non-segmental vitiligo confirmed by a dermatologist.
2. Vitiligo limited to approximately 10% or less of body surface area, with at least one patch that is reported by the participant to have been active in the last 12 months.
3. No other active therapy for vitiligo (or willing to stop current treatment – no washout period required).
4. Able to administer the intervention safely at home
5. Able and willing to give informed consent (or parental/guardian consent in the case of children).

2.4.2. Exclusion criteria

1. Other types of vitiligo (e.g. segmental or universal vitiligo).
2. Patients with vitiligo limited to areas of the body for which NB-UVB light therapy or potent topical corticosteroids would be inappropriate (e.g. around the genitals).
3. History of skin cancer (ever).
4. History of radiotherapy use (ever).
5. Photosensitivity (e.g. lupus, polymorphic light eruption, solar urticaria, chronic actinic dermatitis, actinic prurigo, porphyria or other photosensitivity disorders)
6. Pregnant or breastfeeding women.
7. Current use of immunosuppressive drugs (e.g. e.g. ciclosporin, azathioprine, mycophenolate mofetil, methotrexate)
8. Allergy or contraindication to mometasone furoate or its components.
9. Current participation in another clinical trial or intervention study
10. Marked evidence of Koebner phenomenon.

2.5. Description of interventions

Interventions are potent topical corticosteroid ointment (mometasone furoate 0.1%), hand-held narrowband UVB light therapy (NB-UVB), placebo ointment and dummy NB-UVB light therapy. Participants will receive the following interventions according to their group allocation:

Group A: Topical corticosteroid ointment plus dummy hand-held NB-UVB light
Group B: Placebo ointment plus hand-held NB-UVB light
Group C: Topical corticosteroid ointment plus hand-held NB-UVB light

Participants are advised to use light therapy every other day (3-4 times a week) and apply ointment every day on alternate weeks (one week apply once a day for seven days, the next week do not apply at all).

2.6. Randomisation procedures

Participants are allocated to groups in a ratio of 1:1:1. The randomisation system is created and maintained by the Nottingham Clinical Trials Unit (NCTU). Allocation to treatment groups is minimised, retaining a probabilistic element, by recruiting centre, body region of target lesion (Head and neck, hands and feet, or rest of the body), and age (5 to 16 yrs or >16 yrs).

This is a blinded study with participants, research nurses, principal investigators at site and data analysts being unaware of group allocation.

2.7. Sample size and justification

Standard care is assumed to be topical corticosteroid used as monotherapy and so 'topical corticosteroid 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 topical corticosteroids (plus dummy light)
II. Combination of NB-UVB light therapy and topical corticosteroids compared to topical corticosteroids (plus dummy light).

Assuming that 15% of participants allocated to receive topical corticosteroid (plus dummy light therapy) achieve treatment success as defined by the primary outcome, 372 participants are 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.

A planned review of the sample size was carried out 18 months after recruitment start, after which the DMC recommended recruitment of an additional 76 participants, to bring the total sample size to 516.

2.8. Trial committees

A number of committees were assembled to ensure the proper management and conduct of the trial, and to uphold the safety and well-being of participants. The general purpose, responsibilities and structures of the committees were described in the protocol. However each committee developed its own rules and procedures which might evolve with time.

Trial Management Group: The Trial Management Group (TMG) oversaw the operational aspects of the trial. The TMG met regularly (at least every 2 months) to review the progress of the trial and addressed any issues arising.

Trial Steering Committee: The Trial Steering Committee (TSC) was set up with an independent Chairperson and monitored and reviewed progress of the trial. The independent Trial Steering Committee monitored aggregate data to consider safety and efficacy indications. The TSC may recommend discontinuation of the study if significant ethical or safety concerns arise or if there is very clear evidence of benefit (clinical or statistical) prior to completion of the study. The TSC considered reports from the DMC when making recommendations.

The TSC met prior to the start of the study and agreed its charter.

Data Monitoring Committee: An independent Data Monitoring Committee was established with access to unblinded data (either data by labels or full arm names) to provide independent review and safety oversight. The DMC met or teleconference prior to the start of the study and agreed charter and a provisional meeting or teleconferencing schedule. Only the Data

Monitoring Committee had access to unblinded data until the final outcome assessment has been completed. The DMC reports to the TSC.

2.9. Outcome measures

2.9.1. Primary outcome

Participant-reported treatment success at a target patch of vitiligo (measured by how noticeable the vitiligo is compared to baseline) 9 months after randomisation.

2.9.2. Secondary outcomes

1. Participant-reported treatment success for each body region
2. Investigator-assessed onset of treatment response
3. Percentage repigmentation at 3, 6 and 9 months
4. Quality of life at end of treatment (9 months) and end of follow-up (21 months)
5. Time burden of treatment
6. Maintenance of gained repigmentation during follow-up phase
7. Within trial cost-effectiveness analysis from an NHS perspective (primary) and a family perspective (secondary).

2.10. Two stage database lock

The study team have agreed to plan a two stage lock process, where in the first lock analyses will be restricted to outcomes collected up to 9 months. These are the primary outcome and several other secondary outcomes. Between first and second lock follow up data for 12/15/18/21 months will continue to be collected. All other secondary outcomes will be included in the final analysis after the second lock.

3. GENERAL ANALYSIS CONSIDERATIONS

All analyses will be performed in STATA version 15.0 and no adjustment for multiplicity is planned.

3.1. Analysis sets

ITT set: Participants analysed as randomised, regardless of adherence with allocated group and with imputation of missing data.

Modified ITT set: Participants analysed as randomised, regardless of adherence with allocated group and without imputation for missing data.

Safety set: Participants as per their received treatment. Those who did not report any use of trial treatment will be excluded.
No specific per protocol set will be defined as several sensitivity analyses will be performed on the primary outcome.

3.2. Derived variables

VNS based treatment success

Primary outcome of treatment success is derived from the vitiligo noticeability scale (VNS).

Treatment success is defined as participants reporting that their vitiligo is either "a lot less noticeable" or "no longer noticeable" when asked the question:

"Compared to the start of the study, how noticeable is the vitiligo now?"

More noticeable (1)
As noticeable (2)
Slightly less noticeable (3)
A lot less noticeable (4)
No longer noticeable (5)

Percentage repigmentation based treatment success

Treatment success is also derived from a secondary outcome, percentage repigmentation. There are four options for selecting the level of repigmentation: 0-24%, 25-49%, 50-74%, 75-100%. 75-100% will be classified as a treatment success.

Age at randomisation

Participants' age will be derived using date of randomisation and date of birth recorded.

Onset of treatment response

An onset of response to treatment is defined as *"stayed the same"* or *"improved"* to the question:

"Compared to the start of the study, has there been a change in the vitiligo patch?"

- Stayed the same
- Improved
- Got worse

Loss of maintenance of treatment response

Loss of maintenance of treatment response is defined as *"got worse"* to the question:

"Compared to since you stopped using the study treatments, has there been a change in the vitiligo patch?"

- Stayed the same
- Improved
- Got worse

3.3. Procedures for missing data

Missing data for the primary outcome measure will be reported by treatment group, and patterns of missing outcome data will be explored. Characteristics of participants with and without primary outcome data will also be described by treatment group.

Analysis of the primary outcome will be based on a maximum likelihood estimation method using mixed effect logistic regression model. The maximum likelihood estimation makes use of all data points, so missing values are handled with multiple imputation with chained equations[15].

The following baseline variables will be included in the imputation model:

- Site of target patch (3 regions)
- Skin type
- Age
- Sex
- Hypomelanotic (yes/no/maybe)
- Number of patches - intend to treat (1, 2-3, 4-5, 6+)
- Number of trial patches (1, 2 or 3)

The following post-randomisation variables will also be included in the imputation model as they are closely related to the outcome at 9 months:

- VNS derived treatment success at 3 months
- VNS derived treatment success at 6 months

For the secondary outcome of participant-reported treatment success by body region, a clustered imputation method[16] will be used. The model will include up to 3 assessed body regions at 3 time points. Baseline variables specified above for imputation of the primary outcome and responses at 3 and 6 months from the same body region will be used for the multiple imputation of this outcome.

For the VITIQOL questionnaire, if fewer than 4 items are missing, the score for the missing item will be imputed using the mean of participants who answered that item. If ≥4 items are missing then the participant will be excluded from analysis of VITIQOL scores[11].

For Skindex 29 questionnaire, if fewer than 8 items are missing, missing values are imputed using the mean of the domain scores within the same patient[12]. If ≥8 items are missing then the participant will be excluded from analysis of Skindex-29 scores.

3.4. Model convergence

If a model fails to converge due to complexity, an appropriate alternative model will be used. The estimates may change in format however it won't affect interpretation.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Participant flow

A summary of the number of participants screened, excluded prior to randomisation (with reasons), recruited and followed up will be reported in a CONSORT flow diagram.
A summary of the number and percentage of post-randomisation discontinuations (with reasons) will be presented overall and by treatment arms.

4.2. Baseline characteristics

Patients will be described by treatment group with respect to baseline demographic and vitiligo-related characteristics (including randomisation stratification variables). Numerical variables will be summarised according to their mean values (standard deviation) or median (interquartile range) – depending on skewness of the distribution. Summary of categorical variables will be presented as frequency counts and percentages (calculated using the number of patients for whom data is available as the denominator). Tests of statistical significance of baseline balance/imbalance will not be undertaken.

5. ASSESSMENT OF STUDY QUALITY

5.1. Randomisation

Numbers of participants randomised according to stratification/minimisation variables will be described.

5.2. Adherence

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 total number of treatments is taken from diary logs, unless this is unavailable then it is taken from the Case Report Form (CRF), entered by the nurse after a discussion with the participant. Participants are expected to complete one light session every other day and one ointment session every day on alternate weeks while remaining in the trial.

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).

An expected number of days of non-treatments is assumed to be associated with each grade of erythema. These are grade 1 (0 session), grade 2 (1 session), grade 3 (2 sessions) and grade 4 (3 sessions). The number of episodes of erythema and their respective number of non-treatment sessions will be calculated using these figures and subtracted from the number of expected treatment sessions. Reports of grade 2 erythema will be taken from the diary log, and grade 3 and 4 erythema will be taken from the AE log.

Adherence data will be described using both continuous and categorical forms (for example <=20%, 21-49%, 50-75%, >=75%). Participants whose adherence was more than 75% for both of the two treatments will be defined as adherent and non-adherent otherwise.

6. ANALYSIS OF EFFECTIVENESS/EFFICACY

6.1. Summary of primary and secondary outcomes

Primary outcome

The primary outcome is the participant-reported treatment success (ie, binary treatment success, yes/no) at 9 months assessed at the target patch of vitiligo (must be active) for each participant. Preliminary development and validation of this primary outcome scale has been conducted[1].

Secondary outcomes

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

Assessed at 9 months for the target patch by independent patient reviewers using digital images from trial participants and using the same question for the primary outcome.

Treatment success will be derived on a majority basis from the 3 blinded reviewers.

2. *Participant-reported treatment success by body region:*

Assessed at 9 months, measured using the noticeability question and analysed by body region (A, B and C). Each participant will contribute up to 3 assessed patches from 3 different body regions, regardless of which one was chosen as the target patch.

During the no-treatment follow-up phase, the same question will be 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
- Improved
- Got worse

A response to treatment is defined as "*stayed the same"* or *"improved"*. Analyses for this secondary outcome use investigator-assessed responses because this is deemed to be a more unblinded fashion than the participants assessed, hence less biased and realistic.

4. *Loss of maintenance of treatment response:*

Participant-assessed loss of maintenance of treatment response (including cessation of spread) for the target patch. To be 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?"

- Stayed the same
- Improved
- Got worse

Loss of maintenance of treatment response is defined "*got worse"*.

5. *Percentage repigmentation at 9 months*:

At the end of the 9 month treatment phase, percentage repigmentation will be assessed by blinded independent clinicians using digital images taken at baseline and at 9 months for the target patch.

Percentage repigmentation is also assessed by nurses at 3, 6 and 9 months, for each of the assessed patches, using the baseline images as an aide mémoire. If a digital image of the target patch at follow up is either not available or not useable, nurse assessments will instead be used for the 9-month assessment of percentage repigmentation.

The pattern of repigmentation (perifollicular, marginal, diffuse, mixed, not sure) is also assessed by nurses at the 3, 6 and 9 month clinic visits.

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

- VitiQOL for adults, aged 18 and above. [2];
- Skindex 29 for adults, aged 18 and above. [3] ;
- EQ-5D-5L, for aged 11 years plus adults [4-6];
- CHU 9D for children up to and including 17 years of age [6-9]

7. *Time burden of treatment*:

Participant-reported treatment burden at 3, 6 and 9 months based on average duration and number of treatment sessions and adherence with the treatment schedule. This will be presented separately for light therapy and topical corticosteroid therapy.

6.2. Summary of all outcomes by assessors and associated risk of unblinding

Below is a summary of outcome measures by different assessors and their associated risk of unblinding:

1) Low risk: assessor who had no contact with participants, i.e. blinded reviewer using digital images
2) Medium risk: independent assessor with contact with participants, i.e. nurses in clinic
3) High risk: participant themselves.

Outcome	Who assessed	Risk of unblinding
VNS (Vitiligo noticeability scale)	Participant	High
	Blinded PPI reviewers	Low
Change in vitiligo (Stayed the same/Improved/Got worse)	Participant	High
	Nurse	Medium
Hyperpigmentation (Yes/No)	Nurse	Medium
	Blinded clinician reviewer	Low
Percentage repigmentation (4 level)	Nurse	Medium
	Blinded clinician reviewer	Low

6.3. Primary analysis

The number and proportion 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?") will be reported for each treatment group at 9 months from randomisation.

The primary analysis will be performed on the ITT analysis set, where multiple imputation will be used to account for missing primary outcome data at 9 months.

Randomised groups will be 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 topical corticosteroid alone, and NB-UVB light plus topical corticosteroid with topical corticosteroid alone, will be the risk difference (risk ratio will also be included) in the proportion of participants achieving treatment success at 9 months along with 95% confidence interval and exact p-value.

6.4. Sensitivity analysis of primary outcome

Sensitivity analyses will be conducted as following:

- Further adjustment for any variables with marked imbalance at baseline.

- Analysis on the modified ITT set, i.e. participants who had primary outcome data available at 9 months.

- Investigate the effect of treatment adherence using complier average causal effect (CACE) estimation methods. Complier average causal effect (CACE) analysis will compare outcomes for individuals in each of the two intervention arm who adhered with treatment with individuals in the control arm who would have adhered with treatment. This will be estimated using method[17, 18] such as maximum likelihood approach using a mixture modelling framework or instrumental variables. Adherence status will be treated as a categorical latent variables, with known values in each of the treatment arms.

6.5. Sub-group analysis of primary outcome

Estimated treatment effects on the primary outcome will be described separately by subgroup categories, with interaction coefficients and 95% confidence intervals obtained by including appropriate interaction terms in the primary regression model:

- Body region of target patch: head and neck, hands and feet, and rest of the body

- Children and adults: 5 to 17 years of age (up to 17 years and 364 days) at consent, or >=18 years of age at consent.

- Hypomelanotic: definitely or maybe versus no

- Duration of vitiligo: less than 4 years versus >= 4 years

6.6. Secondary outcomes

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

This data will be presented both in the form of appropriate summary statistics and in graphical form. Between group comparisons will be performed using mixed effect regression model for binary outcome, adjusting by recruitment centre, body region of target patch and age (continuous). The analysis will be performed on modified ITT set where no imputation of missing data is required.

Participant-reported treatment success by body region

This data will be presented both in the form of appropriate summary statistics and in graphical form.

VNS treatment success at 9 months for all assessed patches (up to 3) will be 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 will be conducted with multiple imputation of missing treatment success data at all time points.

Responses from post treatment period (12, 15, 18 and 21 months) will be presented descriptively and not be included in any formal between group comparisons. Analyses of post treatment data will be conducted after the second lock of the database.

Onset of treatment response:
Summary data by all the 3 categories (stayed the same, improved, got worse) will be presented both in the form of appropriate summary statistics and in graphical form, by treatment arm and by timeline (3, 6, 9 months). Cumulative proportion of participants who achieved a treatment response (stayed the same or improved) at target patch will be presented by treatment arm, timeline and body region of the target patch. Analysis of treatment response at 9 months will be analysed using mixed effect regression model for binary outcome, adjusting by recruitment centre, body region of target patch and age (continuous).

Participant reported onset of treatment responses will also be summarised similar to nurse assessed responses. Assessments from non-target patches will also be described similar to target patches.

Loss of maintenance of treatment response
Summary data will be presented both in the form of appropriate summary statistics and in graphical form, by treatment arm and by timeline. This is also presented separately for those who achieved and who did not achieve treatment response by 9 months. Cumulative proportion of participants with loss of maintenance of treatment response will be presented by treatment arm. Depending on quantity of data available at post treatment follow up, this data will also be presented by body region of the target patch. Analyses of post treatment data will be conducted after the second lock of the database.

***Percentage repigmentation at 3, 6 and 9 months*:**
Summary data will be presented for all 4 response categories at all time-points. Analysis of blinded clinician assessed percentage repigmentation at 9 months will be analysed using mixed effect regression model for binary outcome, adjusting by recruitment centre, body region of target patch and age (continuous).
Treatment success based on nurse assessed percentage repigmentation at 9 months, for all assessed patches will be analysed using a multi-level model without imputation of missing data.

The pattern of repigmentation of target patch at all time points will be summarised descriptively.

Quality of life at end of treatment (9 months) and end of follow-up (21 months).
Details of analyses for CHU9D and EQ5D will be found in Health Economic Analysis Plan (HEAP).

Total scores for VITIQOL and Skindex 29 questionnaires at 9 months and 21 months will be summarized by treatment arm using appropriate summary statistics. There is no plan to formally compare the scores between the treatment arms. Analyses of 21 months data will be conducted after the second lock of the database.

Time burden of treatment
Details of analyses will be included in the HEAP.

6.7. VNS outcome validation

Using Vitiligo Noticeability Scale (VNS) data collected in the HI-Light Vitiligo Trial, we will replicate the preliminary validation study of the VNS. At the end of the HI-Light Vitiligo Trial we will have a bank of image pairs that have been assessed for the following outcomes:

1) VNS at end of treatment - assessed by three people with vitiligo
2) Patient-reported global treatment success (successful / unsuccessful) – assessed by three people with vitiligo
3) Percentage repigmentation (quartiles) and presence of hyperpigmentation at end of treatment – assessed by a dermatologist.

We will use these digital images for this validation study.

Building on our previous work[9], we will assess the construct validity of the VNS (compared with global treatment success as reference standard).

For each image pair, a single patient-reported VNS score will be calculated based on the mode (most prevalent response) of the three patient assessors' scores.

We will estimate crude agreement between the scales and the reference standard by converting the five-point VNS and the four-point percentage repigmentation scales into binary measures of success as outlined in section 3.2.

We will test the following hypotheses:

a. there will be a positive association between VNS and global treatment success as reported by patients, with a kappa statistic of ≥0.4
b. the VNS will have better association with patient-reported global treatment success than percentage repigmentation measured by a dermatologist

Analysis: (i) descriptive statistics; (ii) Cohen's Kappa coefficient[10]. The lower kappa statistic is acceptable because we will be comparing two different constructs rather than the single construct assessed.

7. ANALYSIS OF SAFETY

7.1. Adverse events

The study intervention (mometasone furoate 0.1%) is a commonly used drug for which the safety profile is well established and the NB-UVB (Dermfix) is a CE marked device with known side effects[10]. The adverse events section below details what will be captured in this trial for the assessment of safety.

Adverse events will be monitored during clinic visits or at unscheduled visits, if necessary, with the research nurse and or principle investigator for that site. The site investigator will need to distinguish between an SAE that is possibly, probably or definitely related to treatment (i.e. a serious adverse reaction (SAR)/serious adverse device effect (SADE) and an SAE that arises from disease progression or has another cause. All serious events will be captured in the trial.

All adverse events collected are related to trial treatment and non-related adverse events are not reported. Summary data of proportion of participants with any AEs, total numbers of AEs, AEs by MEDDRA coding term names will be presented by treatment arms. Skin thinning and erythema AEs are of particular interest and therefore will be reported separately for children and adults (as per definition for primary outcome subgroup analysis).

Serious adverse events will be summarised in the same format for reporting AEs and all SAEs will also be listed.

All safety data will be analysed on safety set.

7.2. Concomitant medications related to erythema

Participants may take any concomitant medications during the trial. However only medications related to erythema will be reported. Frequency of grade 3 or 4 erythema will be compared descriptively between participants who took any erythema related concomitant medications and those who did not.

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