Home Interventions and Light therapy for the treatment of vitiligo

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SYNOPSIS

Title	Home Interventions and Light therapy for the treatment of vitiligo
Acronym	HI-Light
Short title	HI-Light Vitiligo Trial
Chief Investigator	Dr Jonathan Batchelor
Objectives	To provide information on the comparative effectiveness of topical corticosteroids (mometasone furoate 0.1% ointment) versus (i) home-based NB-UVB light, and (ii) the combination of topical corticosteroids and home-based NB-UVB light therapy for the management of early and limited vitiligo in adults and children. 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 SECONDARY OBJECTIVES • To assess whether treatment response (if any) is maintained once the intervention is stopped. • To compare the cost-effectiveness of the interventions.
Trial 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).
Setting	Participants will be identified from secondary care, primary care and through local advertising. Randomisation will take place in secondary care.
Sample size estimate	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.
Number of participants	516 participants
Eligibility criteria	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). Exclusion criteria 6. Other types of vitiligo (e.g. segmental or universal vitiligo). 7. 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). 8. History of skin cancer (ever). 9. History of radiotherapy use (ever). 10. Photosensitivity (e.g. lupus, polymorphic light eruption, solar urticaria, chronic actinic dermatitis, actinic prurigo, porphyria or other photosensitivity disorders) 11. Pregnant or breastfeeding women. 12. Current use of immunosuppressive drugs (e.g. e.g. ciclosporin, azathioprine, mycophenolate mofetil, methotrexate) 13. Allergy or contraindication to mometasone furoate or its components. 14. Current participation in another clinical trial or intervention study 15. Marked evidence of Koebner phenomenon.
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
Duration of study	Total duration of the study is anticipated to be approximately 51 months and is planned to start recruiting in Q2 2015. Each participant will participate in the trial for 21 months (9 months treatment with 12 months follow-up.
Randomisation and blinding	Participants are allocated to groups in a ratio of 1:1:1. The randomisation system will be created by the Nottingham Clinical Trials Unit (NCTU). Allocation to treatment groups will be minimised, retaining a probabilistic element, by recruiting centre, body region of target lesion (face/neck, hands/feet, or rest of the body), and age (5 to

	16 yrs or >16 yrs). This is a blinded study with participants and research nurses being unaware of group allocation.
Outcome measures	Primary outcome: Participant-reported treatment success at a target patch of vitiligo (measured by how noticeable the vitiligo is compared to baseline) after 9 months of treatment. Secondary outcomes: 1. Investigator-assessed onset of treatment response 2. Participant -reported treatment success for each body region 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).
Statistical methods	The main approach to data analyses will be according to the principle of intention-to-treat. Participants will be analysed in the groups to which they were allocated, regardless of amount of treatment received and without imputation of missing outcome data. The primary estimate of effectiveness will be the difference in proportions of participants demonstrating 'treatment success' at 9 months after randomisation, estimated using appropriate regression modelling adjusting for minimisation variables and presented with 95% confidence intervals. Sensitivity analyses will be used to estimate the effect of treatment adherence, and of imputing missing outcome data. A full statistical analysis plan will be finalised prior to database lock.

ABBREVIATIONS

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

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TRIAL BACKGROUND INFORMATION AND RATIONALE

BACKGROUND

Vitiligo is an acquired, chronic depigmenting disorder of the skin. Vitiligo causes loss of pigment on the affected areas of the skin and/or mucosae and is characterised by milky white, non-scaly macules with distinct margins. This 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.

Vitiligo affects around 0.5-1% of the world's population, although there are no specific prevalence data on vitiligo in the UK. The aetiology of vitiligo is poorly understood and has been disputed for decades. It is still not clear why the melanocytes in vitiligo patches disappear. Several theories have been developed to explain the pathogenesis of what is now considered by some researchers to be a multi-factorial disease[1-6]. In the light of recent genome wide studies, there is now growing evidence that vitiligo has at least in part an autoimmune basis, and this is the target for the development of future treatments [7].

Vitiligo develops at all ages but usually occurs in young people between the age of 10 and 30 [8-11]. Whilst adults and children of both sexes are equally affected by vitiligo, females often present for treatment more frequently; likely due to the greater social stigma women and girls affected by this condition face [10,12].

The most commonly affected initial sites in non-segmental vitiligo are usually the face, followed by the neck and trunk[13]. The cosmetic disfigurement of this seemingly inconsequential skin disease has a major impact on quality of life[14]. Patients with vitiligo experience a number of psychological problems such as shame, depression and anxiety, which leads to low self-esteem and social isolation[15,16]. Mood disturbances are common, particularly in teenagers. Vitiligo beginning in childhood can be associated with significant psychological trauma that may have a long lasting effect on personal self-esteem.

Despite being a common condition, which has a major negative impact on the lives of its participants, there are no studies on the natural history of vitiligo. Therefore, treatment recommendations are based on consensus view[17]. Current clinical guidelines for the diagnosis and management of vitiligo recommend narrowband UVB (NB-UVB), tacrolimus topical corticosteroids and combination therapies[17,18]. However, the evidence base for treatments is currently poor [19].

In the UK, NB-UVB is almost exclusively available in secondary care, often used for widespread vitiligo, and requires regular visits to the hospital[17]. Currently, there are various devices available for the delivery of NB-UVB at home. The choice of the device is usually based on the size and location of the vitiligo and the percentage of the affected body surface[20]. Only one small pilot randomised controlled trial (RCT) has been conducted comparing hand-held NB-UVB to dummy devices for the management of vitiligo[21]. This pilot trial demonstrated that people with vitiligo were keen to take part in a trial of home light therapy and that the devices were safe and well tolerated when used to treat children and adults at home.

The HI-Light Trial will be the first large-scale multi-centre, pragmatic RCT to evaluate the use of topical corticosteroids and NB-UVB at home. A nested mixed methods process evaluation will also be conducted 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 in a home setting. This process evaluation is described in detail in Appendix 1.

RATIONALE FOR THE HI-LIGHT VITILIGO TRIAL

Importance of the topic to patients and healthcare practitioners

Priority topics for future vitiligo research that are important to patients and healthcare practitioners were identified and prioritised through a James Lind Alliance Priority Setting Partnership in 2010[22]. The HI-Light 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; as such the HI-Light trial will enrol both children and adults.

Importance of treating early and limited disease

Histopathology findings for vitiligo differ according to the three phases of the disease: early stages, established patches and long standing patches. Established vitiligo and long standing patches show absence of melanin in the epidermal layer and otherwise normal skin. This has led some to believe that early treatment of vitiligo during the early stages of the disease is likely to be most beneficial. This has also been suggested by clinical studies[23]. For this reason, participants will be required to have at least one patch of vitiligo that has either appeared or worsened in the last 12 months.

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

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 participants with eczema and psoriasis. Early reports suggest that these are well tolerated and effective [24-27].

There are several benefits of using hand held NB-UVB devices for diseases like vitiligo with limited skin involvement[28] including:

- reduction in attendance at hospital and associated time and travel costs for patients
- only treating involved areas, thus sparing uninvolved skin
- treatment of vitiligo in children at the early stage of their disease, when usually more extensive whole body phototherapy is not indicated
- low cost of the devices compared to bulky, expensive, whole body units suited mainly for widespread disease.

Should a hand-held device prove to be effective and safe for the treatment of focal and/or early vitiligo, this could be an important addition to the treatment options available to patients/people with limited disease (found on the face, hands, ears, or lips), early stages of the disease, or for patients wishing only to treat specific patches.

Existing evidence

Despite being a common condition, which has a major negative impact on the lives of its participants, there are no studies on the natural history of vitiligo.
A Cochrane systematic review looking at interventions for the treatment of vitiligo was updated in 2010[19]. This review identified 57 trials covering 68 different treatment options. However, the quality of the trials included in the review was generally poor, making it difficult to make firm recommendations based on the current evidence, although the use of NB-UVB light therapy was generally supported and the combination of light therapy with other active interventions appeared to be more effective than monotherapies.

Patient Influenced Outcome Measures

A systematic review of outcomes used in previous vitiligo trials and a survey of patients and clinicians' views regarding choice of outcomes to be used in vitiligo research found a discrepancy between what is measured in vitiligo trials and what outcomes patients feel are important for informing their treatment decisions[29].

A recent international e-Delphi consensus exercise has established core outcome domains for vitiligo trials. Outcomes that should be included 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.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Topical corticosteroid - mometasone furoate 0.1% ointment

Topical corticosteroids are classified as mild, moderate, potent or super potent (BNF, edition 67, March 2014) and it is generally recommended that either a potent or super potent topical corticosteroid is used for the treatment of vitiligo[18].

Mometasone furoate 0.1% ointment, a potent corticosteroid, will be used in the HI-Light trial. Mometasone furoate 0.1% ointment has been chosen because it is the most commonly-used topical corticosteroid in vitiligo in both adults and children in the UK[30], and it is specifically recommended in the European Clinical Guidelines for the management of vitiligo(23).

Further chemical and pharmacological properties of mometasone furoate 0.1% ointment are provided in a separate Summary of Product Characteristics document (SmPC).

The Elocon brand of mometasone furoate 0.1% ointment will be used for the purposes of this trial.

Manufacture of Mometasone furoate 0.1% ointment

Elocon Ointment (Merck, Sharp and Dohme Ltd PL00025/0578) will be used in this trial. It will be referred to as mometasone fuorate 0.1% ointment throughout the protocol.

Packaging and labelling of Mometasone furoate 0.1% ointment

For blinding purposes, active ointments will be repackaged into plain tubes by Nottingham University Hospitals NHS Trust MIA(IMP): 19162. The manufacture will be in accordance with cGMP for the packaging of ointments. The tubes will be labelled according to Annex 13 of Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007. Labels will also state home storage conditions for the participants. Each tube will be assigned a container number that will facilitate identification of the contents. A QP will release the blinded IMP tubes for use in the trial.

Further details of the manufacture of the blinded packs of active ointments are provided in a separate simplified IMPD.

Storage, dispensing and return of Mometasone furoate 0.1% ointment

Mawdsley Brookes and Company Ltd MIA (IMP) 741 will receive blinded packs of active and placebo ointments from Nottingham University Hospitals NUH Trust MIA(IMP): 19162. They will be stored at Mawdsleys for distribution direct to participants' homes. They will be held in a restricted access warehouse only accessible to authorised personnel. Trial supplies will be kept separately to other supplies and labelled accordingly (with trial labels). The trial treatment will be stored at Mawdsleys below 25C.

Upon randomisation of a participant, Mawdsleys will be notified via a web-based system (maintained by the trial coordinating centre) of the container numbers of the ointment allocated to the randomised participant. They will add participant study number and initials to the IMP tubes and pack them together with the assigned light. Distribution will be recorded on the appropriate accountability forms.

The final product (ointment and light) will be assessed by a QP who will approve for despatch the blinded trial treatment pack, for use in the trial.

Trial packs (including ointment and light) will be sent direct to the participant's home, using a tracked and signed for courier service. Receipt of the IMP and light will be confirmed by the participant. Prior to receipt, participants will have received full training (both written, oral and through a training video) from the research team on use of the trial interventions.

The quantity of ointment supplied at time of randomisation will be two x 90g tubes. This amount is expected to be sufficient to last the duration of the trial, however participants will be able to request more ointment at the 6 month follow-up appointment, and a procedure for an additional supply will be in place. A request for an additional supply of the IMP will be notified to Mawdsleys and distributed in a similar manner to the first supply.

The total dosage needed by a participant over the course of the 9 month treatment phase is not expected to exceed 270g, and a procedure will be in place to capture any instances where a trial participant has requested more than this amount. Before being prescribed additional ointment, checks will be made to establish the need for additional supplies, and if necessary, a consultation with a dermatologist associated with the trial will be arranged to

determine whether or not the participant is using the ointment correctly and has a genuine need for additional supplies.

Trial treatment must not be used for any other purpose than the present study. Unused ointment and devices will be returned to the recruiting site at the 9 month appointment. Unused ointment will be returned to the local pharmacy for disposal according to their local procedures. Returned trial medication that has been supplied to a participant must not be re-supplied to a different participant.

Known Side Effects of Mometasone furoate 0.1% ointment

Known adverse reactions to mometasone furoate 0.1% include: infection, folliculitis, paraesthesia, burning sensation, contact dermatitis, skin hypopigmentation, hypertrichosis, skin striae, acneiform dermatitis, skin atrophy, pruritus and application site pain, according to the SmPC.

Topical corticosteroids are used to treat a very wide range of skin conditions, including common conditions such as eczema and psoriasis, as well as vitiligo. The risk of adverse effects with topical corticosteroids of low or moderate potency is extremely low. The risk of adverse effects for potent topical corticosteroids (such as mometasone furoate) is slightly higher, but it is widely acknowledged that the fear of adverse effects is usually disproportionately high, given the relative infrequency with which such adverse effects are observed. Despite the ubiquity of topical corticosteroids in dermatological therapeutic practice, there is surprisingly little evidence to quantify the risk of adverse effects accurately. Guidelines often suggest that potent topical corticosteroids should be used only under close clinical supervision, particularly when used in children on anatomical sites where the skin is thinner and therefore more prone to adverse effects such as atrophy.

Reference source: SmPC for Elocon (mometasone furoate 0.1%) ointment (Section 4.8).

DETAILS OF PLACEBO INTERVENTIONS

Placebo topical ointment

The placebo ointment will be an inert ointment (white soft paraffin) present in the base used to formulate mometasone furoate 0.1% ointment. Further details of the manufacture of the placebo ointment will be provided in a separate simplified IMPD.

Manufacture of Placebo Topical Ointment

The placebo ointment will be manufactured, supplied, packaged, labelled and QP released to provide blinded treatment packs and distributed in the same way as the active IMP.

Packaging and labelling of Placebo Topical Ointment

Packaging and labelling of the placebo topical ointment will be the same as the active IMP.

Storage, dispensing and return of Placebo Topical Ointment

Storage, distribution and return of the placebo topical ointment will be the same as the active IMP.

Known Side Effects of Placebo Topical Ointment

None known.

DETAILS OF MEDICAL DEVICE

Medical devices used in this study will be used in accordance with their marketing licence and are not modified in any way with the exception of adding a filter to the dummy device. Therefore this is not a study that comes under the Medical Devices Directive as we are not seeking to alter the marketing authorisation of the device.

Device Description: Hand-held narrow band UVB (NB-UVB) light therapy device

NB-UVB light therapy is now the most common form of phototherapy used to treat vitiligo. Narrow-band refers to the wavelength of ultraviolet (UV) radiation, 311 to 312 nanometers (nm). To date, UVB treatment has usually been delivered in a hospital setting and involves irradiation of the entire body, making it unsuitable for limited disease.

Hand-held NB-UVB units are portable and light weight devices. Several brands are CE marked and approved for use in the UK. For the HI-Light Trial, a Dermfix™ unit (pictured) is being used, within its licensing agreement. The Dermfix™ phototherapy unit has an on/off switch and an external digital timer.

All interventions will be used as monotherapy or in combination.

Manufacture of Hand-held NB-UVB devices

The Dermfix™devices (Model 1000MX, CE marking: 0123) are manufactured by Dermfix Ltd (www.dermfix.com) and will be supplied by Androv Medical. The device will be used in accordance with its licensed use.

All NB-UVB devices will be tested by the Medical Physics Department at Nottingham University Hospitals NHS Trust prior to distribution. This will include electrical safety testing and establishing the output of the devices is in accordance with the treatment schedule. There will be no further testing of the devices over the 9-month treatment period.

If a device is found to be more than ±10% of the mean output, then the device will be returned to the manufacturer and a replacement device acquired.

Packaging and labelling - Hand-held NB-UVB Devices

Hand held NB-UVB devices and dummy devices will be labelled for the trial by the Medical Physics Department at the Nottingham University Hospitals NHS Trust Medical Physics Department. Labelling will conform to the standard trial labels and will include the device number.

Storage, supply and return of the hand-held NB-UVB device

Tested and labelled devices will be sent to Mawdsley Brookes and Company Ltd (tracked by detailed distribution logs held by the trial coordinating centre, medical physics department and Mawdsleys). They will be stored at Mawdsleys for distribution direct to participants' homes. They will be held in a restricted access warehouse only accessible to authorised

personnel. Trial supplies will be kept separately to other supplies and labelled accordingly (with trial labels).

Upon randomisation of a participant, Mawdsleys will be notified via a web-based system (maintained by the trial coordinating centre) of the device number of the light to be distributed and pack it together with the assigned ointment. Supply will be recorded on the appropriate accountability forms. The final product (ointment and light) will be assessed by a QP who will approve for despatch the blinded trial treatment pack for use in the trial.

Trial packs (including ointment and light) will be sent direct to the participant's home, using a tracked and signed for courier service. Receipt of the pack will be confirmed by the participant. Prior to receipt, participants will have received full training (both written, oral and through a training video) from the research team on use of the trial interventions.

Trial treatment must not be used for any other purpose than the present study. Devices will be returned to the recruiting site at the 9 month appointment.

Known Device Effects

NB-UVB light

Known adverse reactions to NB-UVB light 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.

The risk of carcinogenicity with NB-UVB therapy is still unclear, as there is limited evidence on which to base risk estimates. Some follow-up studies suggest that NB-UVB confers a very minimal risk of carcinogenicity[31]. The British Association of Dermatologists' guidelines for diagnosis and management of vitiligo advise that in view of the greater susceptibility of vitiliginous skin to sunburn and possible photo-damage (due to absence of melanin), safety limits for NB-UVB for the treatment of vitiligo have an arbitrary limit of 200 treatments for skin types I–III. This could be higher for darker skin types at the discretion of the clinician and with the consent of the participant[17,32]. However, this limit is based mainly on specialist consensus, and more research is needed to establish the optimum number of treatment sessions as well as a maintenance regimen for vitiligo.

DETAILS OF DUMMY MEDICAL DEVICE

The dummy NB-UVB light devices will be identical to the normal Dermfix™ device unit, but the plastic cover over the bulb is replaced with one that prevents the ultraviolet light from being transmitted to the skin. Experience from our external pilot trial[21] has shown that use of a dummy device is acceptable to patients, is effective in blocking the UVB radiation and is at least partially effective in masking treatment allocation from participants (70% of participants and 40% of research nurses guessed their treatment allocation correctly in the pilot trial – largely on the occurrence (or not) of side effects over the course of the trial).

Manufacture of dummy NB-UVB Devices

The dummy NB-UVB device will be the same as the active device: Dermfix™ (Model 1000MX, CE0123), but with a transparent cover in place that blocks transmission of UVB light to the skin. This cover will be manufactured and put in place specifically for the trial by the manufacturer of Dermfix ™, Androv Medical Ltd.

Nottingham University Hospitals NHS Trust Medical Physics Department will conduct electrical safety testing of the devices, and will ensure that there is no UVB emission from the placebo devices by testing output prior to distribution.

Packaging and labelling of dummy NB-UVB Devices

Packaging and labelling of the dummy NB-UVB Devices will be the same as the Hand-held NB-UVB devices.

Storage, supply and return of dummy NB-UVB Devices

Storage, supply and return of the dummy NB-UVB devices will be the same as the hand-held NB-UVB devices.

Known Side Effects of dummy NB-UVB Devices

None known.

TRIAL OBJECTIVES AND PURPOSE

PURPOSE

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

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

SECONDARY OBJECTIVES

- To assess whether treatment response (if any) is maintained once the intervention is stopped.

- To compare the cost-effectiveness of the interventions.

TRIAL DESIGN

TRIAL CONFIGURATION

The proposed trial is a multi-centre 3-arm, double-blinded, randomised controlled trial. Participants will be randomised to one of three treatment groups (see figure 1):

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 will receive treatment for 9 months, when the primary outcome will be assessed. Primary outcome assessment at 9 months was chosen to reflect the slow re-pigmenting nature of vitiligo. Nine months of treatment is sufficiently long to ensure that any patches that have started to respond to treatment have had time to reach a clinically meaningful treatment response prior to primary outcome assessment.

Long-term follow-up will continue via questionnaire for a further 12 months post-randomisation.

Endpoints

The following endpoints refer to 'target patches of vitiligo' (for primary outcome assessment) and additional 'assessed patches of vitiligo' (for secondary outcome assessment).

The target patch of vitiligo must have been active in the last 12 months. Active status is based on participant self-report, though patches will also be assessed by the research nurse according to the classifications outline by Benzekri et al 2013 [33]. The authors reported that 93% of active lesions were hypomelanotic with poorly defined borders, and 85% of stable lesions were amelanotic with sharply demarcated borders, suggesting that this might be a useful indicator of disease activity.

If a patient has more than one active patch, then the target patch will be chosen as being the one in which the patient would most like to see an improvement.

Since vitiligo is reported to respond differently at different body regions, secondary outcomes will be reported by body region.

Assessed patches will be chosen by the participant and nurse prior to randomisation and participant may identify up to three patches for assessment.

Each assessed patch must be in a different body region.

- Region A: face & neck
- Region B: hands & feet
- Region C: rest of the body

Digital images of the target patch, taken at baseline and 9 months, will also be used by blinded independent assessors to:

- Assess the primary outcome of treatment success
- Assess global treatment response
- Assess % repigmentation at 9 months

Primary endpoint

1. Participant-reported treatment success at 9 months:

The primary outcome will be assessed at the target patch of vitiligo for each participant.

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)

Preliminary development and validation of this primary outcome scale has been conducted[34].

Digital images of the target patch (taken at baseline and 9 months) will be assessed by independent assessors to provide blinded assessment of the primary outcome.

Secondary endpoint

2. *Onset of treatment response:*

Participant and investigator-assessed onset of treatment response (including cessation of spread) for each assessed patch of vitiligo in each of the three body regions. To be assessed at 3, 6 and 9 months using the following question (asked first of the participant and separately of the nurse):

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

- Stayed the same (2)
- Improved (3)
- Got worse (1)

3. *Participant-reported treatment success, analysed by body region:*

Assessed at 3, 6, 9 months, measured using the noticeability question (primary endpoint measure), and analysed by body region (A, B and C).

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.

4. *Percentage repigmentation at 3, 6 and 9 months*:

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

As back-up, % repigmentation will also be assessed by nurses at 3, 6 and 9 months, for each of the assessed patches, using the baseline images as an aide mémoire. If there is a problem with the digital images of the target patch, nurse assessments will be used for the 9-month assessment of % repigmentation.

The pattern of repigmentation (perifollicular, marginal, diffuse, mixed, not sure) will also be assessed by nurses at the 3, 6 and 9 month clinic visits. This will be recorded for descriptive purposes.

5. *Quality of life at end of treatment (9 months) and end of follow-up (21 months).*
   - VitiQOL for adults, aged 18 and above. [35];
   - Skindex 29 for adults, aged 18 and above. [36] ;
   - EQ-5D-5L, for aged 11 years plus adults [37-39];
   - CHU 9D for children up to and including 17 years of age [39-42]

6. *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. To be presented for light therapy and topical corticosteroid therapy separately.

7. *Maintenance of treatment response:*

Patient reported maintenance of treatment response for each assessed patch of vitiligo in each of the three body regions. To be asked in the long-term follow-up period in the 12, 15, 18 and 21 month questionnaires:

"Thinking now about since you stopped using the trial treatments, has the vitiligo patch:"

- Stayed the same
- Improved
- Got worse

8. *Within trial cost-effectiveness analysis from an NHS perspective (primary) and a family perspective (secondary) – including treatment and follow-up phases*

This will be achieved using incremental cost analysis, and estimations of quality-adjusted life years. Cost-effectiveness will be estimated as incremental cost per successful treatment and cost-utility will be estimated as incremental cost per QALY. (See cost-effectiveness section for details).

Safety endpoints

Proportion of adverse device effects and adverse reactions to the topical corticosteroid and NB-UVB during the treatment phase.

Stopping rules and discontinuation

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and the funder (NIHR HTA) as appropriate in making this decision.

RANDOMISATION AND BLINDING

The randomisation system will be created by the Nottingham Clinical Trials Unit (NCTU). Allocation to treatment groups will be minimised, retaining a probabilistic element, by recruiting centre, body region of target lesion (face/neck, hands/feet, or rest of the body), and age (5 to 16 yrs or >16 yrs).

Participants, research nurses, principal investigators and data analysts will be blinded to treatment allocation by use of dummy UVB devices and a placebo for TCS. Only the NCTU IT Manager (who creates the treatment allocation schedule), the medical physics staff and NCTU QA staff, responsible for testing and checking the blinding of the devices, will be aware of the allocation of active / placebo treatment. Participants will be randomised by a research nurse via a randomisation website, held on a secure web server at NCTU, which will allocate participants to a treatment group. This will take place after the patient has given consent for participation in the trial, digital photographs have been taken, and results of the MED test are known, confirming all eligibility criteria for the trial are met.

Whilst every effort will be made to maintain blinding of the trial interventions, it is possible that blinding may be compromised, particularly if participants experience adverse reactions to the interventions.

Since there is a risk that participants may be able to guess their treatment allocation, additional measures will be taken in order to limit the impact of this in the trial results:

i) The primary outcome and some secondary outcomes will also be assessed using digital images taken at baseline and at 9 months. The images will be assessed by independent assessors (both independent clinicians and patients), who will be blinded to the treatment allocation.

ii) Information for potential participants will emphasise that all participants receive at least one active treatment for their vitiligo; thus reducing potential detection bias and unblinding due to lack of treatment response (which was the main reason for guessing treatment allocation correctly in the pilot trial).

On exit from the trial (at the time of the 9 month clinic visit), participants and research nurses will be asked if they believe they were unblinded, and if yes, which treatment they thought had been allocated to the participant. This may be used to inform interpretation of the trial results.

Maintenance of randomisation codes and procedures for breaking code

Only the IT staff at NCTU will be aware of the allocation of participants to groups.

In case of a medical emergency where an active treatment of the ointment or the device would need to be stopped, active treatment of both treatments should be assumed. The participant should be instructed to stop using their trial interventions, either permanently or until the medical event has been resolved. As a result, unblinding of the treatment allocation is unlikely to be necessary.

If knowledge of a participant's treatment allocation is necessary, the local principal investigator or his/her delegate will be able to log into the online blind-break system, which will be available 24 hours a day. On this system they will have to specify why the blind needs

to be broken, and an audit trail of any instances of breaking of the code will be maintained. Details of the date, name of person requesting the blind to be broken, a reason why, and any other relevant information will be recorded.

TRIAL MANAGEMENT

The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (12/24/02). It is sponsored by the University of Nottingham, and will be managed and co-ordinated at the Nottingham Clinical Trials Unit, with support from the Centre of Evidence Based Dermatology in Nottingham.

The Trial Steering Committee (TSC) will meet at least once a year and will provide independent oversight of the trial on behalf of the trial sponsor.

The Data Monitoring Committee (DMC) will meet at least once a year to assess safety, effectiveness and futility of the study and will report to the TSC.

The Trial Management Group (TMG) will meet more frequently, at least every two months, and will be responsible for the day-to-day management of the trial. The TMG will report to the TSC at their meetings.

The Chief Investigator has overall responsibility for the study and shall oversee all study management and will be responsible for monitoring of safety outcomes and reporting arrangements. The Deputy CI will also maintain oversight of study management with a trial manager responsible for the day to day running of the study.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration: Individuals will participate in the trial for 21 months: The treatment period lasts 9 months, followed by a 12 month long term follow-up.

Study Duration: The recruitment period for the trial is anticipated to begin in Q2 2015 and to last for 18 months.

End of the Trial

The end of the study will be the last 21 month questionnaire of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Randomisation will take place in secondary care hospitals. However, GP practices and other local hospitals in the surrounding area will be approached to act as Patient Identification Centres (PICs). GP surgeries will send out invitation letters to patients who may be eligible for the trial. Each GP surgery will be randomised to either include in the letter details of a basic trial website, or an enhanced trial website. This GP surgery randomisation is part of the MRC START in HI-Light embedded sub-study which is looking at effects of a multimedia resource on recruitment. Further details can be found in Appendix 2 to the protocol.

Potential participants will also be identified through direct local advertising (including but not limited to e-mail distribution lists held by the Centre of Evidence Based Dermatology radio and TV interviews, websites and articles). If other potential sources for recruitment become apparent during the trial, these will also be included following REC approval. A dedicated website will be available for the purpose of this trial.

For participants identified through secondary or primary care, the initial approach will be from a member of the patient's usual care team (which may include the investigator), and information about the trial will be on display in the relevant clinic areas. The initial approach may be made by invitation letter or in person at a clinic. All interested potential participants or their parent/guardian will need to complete a reply slip, either paper or online, in order to be pre-screened by a member of the research team. Potential participants/parents/guardians are made aware that any non-identifiable information collected on the reply slip will be stored, anonymously, on a secure database to collect data about the population coming forward as interested in the trial.

Once a reply slip is returned to the trial team, the investigator or their nominee, e.g. from the research team, will pre-screen the potential participant (or their parent/guardian) and inform them of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, consent forms, and training sessions/information. However, consent forms, information sheets, training information and participant questionnaires will not be available in languages other than English, as participant's ability to read and understand English will be important to ensure their safe participation in the trial and appropriate use of the trial treatments.

It will be explained to the potential participant/parent/guardian that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time without giving a reason. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

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 (assessed pre-randomisation), 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 (with parental/guardian help for small children or those wishing to treat a patch not accessible for self-treatment).

5. Able and willing to give informed consent (or parental/guardian consent in the case of children (under 16s)).

Other concomitant treatments and medications, with the exception of those listed under 'Exclusion criteria' are acceptable.

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 (eg. dermatomyositis)).

6. Pregnant, breastfeeding or likely to become pregnant during the 9-month treatment period (largely due to the time commitment of the treatment and logistics of the trial).

7. Current use of immunosuppressive drugs (e.g. ciclosporin, azathioprine, mycophenolate mofetil, methotrexate, systemic tacrolimus).

8. Allergy or any contraindication to mometasone furoate or any of its components (e.g any cutaneous bacterial, viral or fungal infections in the area to be exposed to trial treatments), as listed in section 4.3 of the SmPC.

9. Current participation in another clinical trial or intervention study.

10. Marked evidence of Koebner phenomenon.

Only one participant will be recruited per family. If more than one person is eligible for entry into the trial, the choice of who should take part will be made by the family members themselves. This decision has been made to prevent accidental confusion of blinded trial treatments for people living in the same household.

Expected duration of participant participation

Trial participants will participate in the study for up to 21 months.

Removal of participants from therapy or assessments

Participants may be withdrawn from the trial or the intervention(s) either at their own request or at the discretion of the investigator. If a participant wishes to withdraw from one of more of the trial interventions, they may do so, but follow-up will continue in the normal way unless the participant chooses to withdraw from the trial completely.

Participants will be made aware that withdrawal from either treatment of follow-up will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw, the data collected to date cannot be erased and may still be used in the final analysis.

Participants who withdraw after randomisation will not be replaced.

Informed consent

All participants will provide written informed consent, both for participation and retention of the trial data. The Consent Form will be signed and dated by the participant before they enter the trial. The Investigator (or designee) will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator (or designee) will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, one will be filed in the participant's medical records, and a fourth will be sent to the participants GP.

Where the Participant is under age 18, an age-appropriate Participant Information Sheet will be provided. Parental or legal guardian consent will be obtained for all participants under the age of 16. The child may give their assent on the same consent form if they wish to. In the event of any disagreement between the parent and child, the child will not enter the study.

If any trial participant turns 16 years of age during the active treatment phase of the trial, the Investigator (or designee) will obtain a Consent Form, signed by the participant, at their next trial clinic visit. The participant will have an opportunity to have the trial and consent form re-explained to them. If the participant does not wish to consent themselves upon turning 16, the participant will be withdrawn from the trial.

Should there be any subsequent amendment to the final protocol, which might affect participation in the trial, continuing consent will be obtained using an amended consent form, which will be signed by the participant and/or parent or legal guardian.

TRIAL AND TREATMENT REGIMEN

TRIAL REGIMEN

Pre-Trial contact (telephone call/email)

On receipt of potential participants' reply slip, an age-appropriate information sheet(s) will be sent and a member of the research team will make contact, either by telephone, letter or e-mail. An overview of the trial will be given and provisional eligibility will be established. If the participant is potentially eligible and willing to attend for a screening visit, an appointment with the research nurse will be made at the closest participating hospital.

Clinic Visit 1- Screening and Consent

During this clinic visit the participant (and their parent/legal guardian, if under 16 years of age) will be given the opportunity to discuss the trial further with a member of the trial team and any questions they have will be answered. Informed consent will be obtained from the participant, or parent/legal guardian in case of a child, before undertaking any trial related procedures.

The Screening visit will include the following activities:

- Confirmation of diagnosis and suitability of NB-UVB light therapy / potent topical corticosteroid treatment by a dermatologist
- Confirmation of other eligibility criteria
- Informed consent
- Conducting a minimum erythema dose (MED) by shining controlled doses on NB-UVB light on the skin, as per standard clinical practice.
    - The MED test will be performed for each participant prior to commencing the treatment, in order to check for rare, but potentially serious light sensitive skin conditions (e.g. polymorphic light eruption) to confirm eligibility.
    - Participants will receive doses of NB-UVB using a MED tester at the 'screening and consent visit' and will be asked to return the following day for assessment of the MED test results.
- Assessment of participant's skin phototype

Pregnancy status will be assessed by self-report during screening for the trial, but a pregnancy test will not be required, as standard clinical practice is to continue to use topical corticosteroids and NB-UVB light therapy during pregnancy as systemic absorption of mometasone furoate, and therefore risk of side-effect to the unborn foetus, is extremely low[43,44]. The main motivation for excluding pregnant and breastfeeding women is largely because of the time burden of the treatment, which would be incompatible with the demands of pregnancy and breastfeeding.

If a participant becomes pregnant during the trial then the recruiting PI (in discussion with the participant) will make a clinical judgement as to whether or not treatment(s) should be withdrawn for the remaining period of the trial. Unless consent for participation in the trial is withdrawn, participants will remain in the trial and provide follow-up data, regardless of whether treatment has been stopped or not.

Clinic Visit 2- Randomisation and start of treatment (Baseline)

Participants will return to the hospital the day after administration of the MED test, so that their MED results can be read.

If potential participants are suitable to receive NB-UVB light therapy, they will be randomised using the web-based randomisation system. If not eligible for the trial, participants will be treated as per routine care.

Other Clinic Activities at Visit 1 or Visit 2

In addition to the above activities, the following will take place at either visit 1 or visit 2, depending on local need, availability and participant preference:

- Confirmation of vitiligo patches to be designated as the 'assessed patches of vitiligo' (a maximum of three patches, one per body region (region A: face & neck; region B: hands & feet; region C: rest of the body). Designation of which of the assessed patches will be considered the 'target patch', which will be used for the primary outcome.
- Collection of outcomes and baseline data (including digital images of the vitiligo – performed by a medical photographer). Baseline images are required, and no participant can be randomised until they have been taken.

- Health resource use and Quality of Life questionnaires (VitiQOL, Skindex, EQ-5D-5L for adults, CHU-9D for children)
- Training session on how to use the trial interventions, how to complete the necessary paperwork, and how to monitor and respond to adverse reactions and adverse device effects.

Training in the use of the NB-UVB light devices may vary according to local practice. This will be delivered either by the research nurses or local phototherapy teams trained in the use of the devices. A training video and information booklet, covering the information given during the training sessions, will be given to participants on entry into the trial.

The training session will include guidance specific to both the NB-UVB light treatment and the topical corticosteroid ointment. Demonstrations of how to use the devices will be delivered using a dummy device, and demonstrations of how to use topical corticosteroids will be delivered using white soft paraffin or an equivalent emollient. Training will include the following:

- Safe operation of the hand held phototherapy device, including safe treatment of patches near the eyes.
- Correct administration of treatment according to the treatment protocol, which includes adjustment of the treatment session time according to the erythema response for NB-UVB light, and adjustment of the topical corticosteroid use if side effects are experienced.
- Accurate recording of treatments i.e. how to fill in the treatment diary, possible short term side effects and how to deal with them including the contact details of appropriate people at the recruiting hospital who will be able to offer support in the case of side effects.
- A supervised treatment session with a dummy device, followed by an application of the placebo ointment (white soft paraffin) will also be undertaken.

If the participant is a child, the carer or parent will be required to accompany him/her during the training session and supervised treatment session in order to be taught how to administer the treatment at home. Adults wishing to treat the face, or an inaccessible area of the body, will also require assistance in administering the interventions.

If the participant or their parent/carer does not demonstrate competence in administering treatment, then the training programme will be extended or repeated. A participant will not be able to be randomised onto the study until they (or their parent/guardian) has demonstrated full comprehension of proper usage of the treatments.

Scheduled Interim Follow-Up Visits and telephone calls

Telephone support at two weeks

Participants will be telephoned by a member of the trial team in order to check that treatments have been received, that the participant has successfully started treatment and to check that participants are completing the treatment diary correctly.

3, 6 and 9 month clinic visits

These face to face visits will be conducted at the recruiting hospital and will be used to collect outcome assessments and information about treatment adherence, monitor adverse reactions, and support and reinforce use of the interventions.

In addition to the above, the 9 month visit will also include digital images of the vitiligo, and completion of the quality of life scales. Whilst every effort should be made to complete 9 month visits face to face, if a participant is not able to attend the 9 month clinic visit, efforts will be made to collect the data remotely (by phone, online or post).

Throughout the treatment phase, participants will complete a diary that records treatment adherence, adverse reactions and health service resource use.

If a participant experiences difficulties with their treatments or a side effect for which they need advice or consultation, they will be provided with a phone number which they may contact during clinic hours, to speak to a member of the research team. An additional unscheduled appointment may be scheduled with a member of the research team to address the participants concern/monitor safety, as appropriate.

Long-term follow up

At the end of the treatment phase (9 months), participants will enter the long-term follow-up phase. During this time, participants will be sent a questionnaire (on-line or paper) every 3 months (12, 15, 18 and 21 months) to capture long-term treatment effects. At 21 months post randomisation, quality of life will also be assessed, along with qualitative feedback on use of the interventions and participation in the trial.

Due to trial timelines, participants recruited towards the end of the recruitment period may not receive the 21 month follow-up questionnaire.

During the follow-up period, trial participants will be able to contact the trial management team at the coordinating centre for assistance with the questionnaires (technical support or clarification). The trial management team will send text reminders to participants that questionnaires are ready for completion and follow-up (via telephone, text message, letter or email) outstanding questionnaires to achieve maximum compliance.

Figure 1 – flow diagram

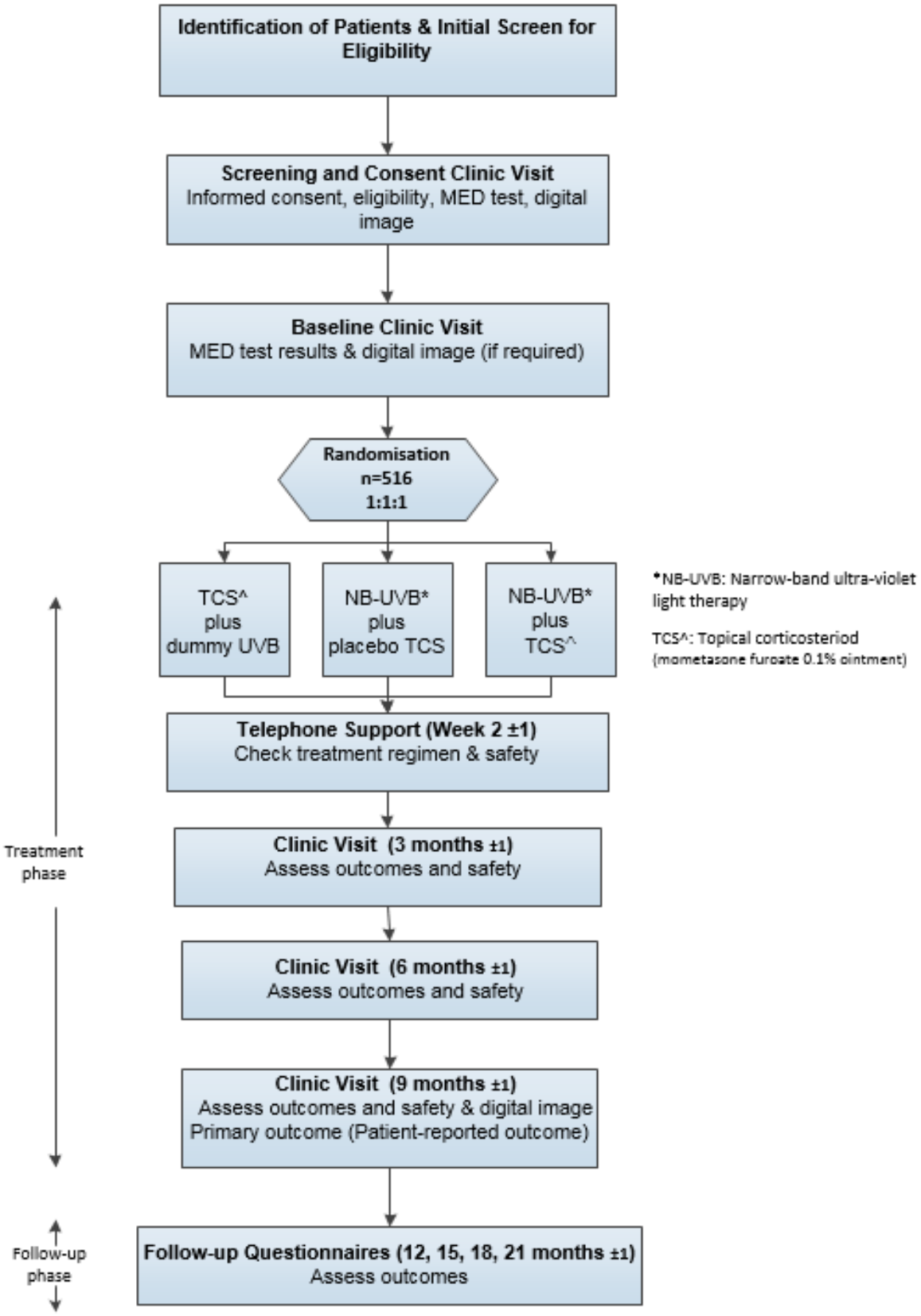

Table 2- Study Assessments

Outcome collected	Pre-screen	Visit 1 - screening	Visit 2 - baseline	Telephone Screen (2 weeks)	Visit 3 (3 months)	Visit 4 (6 months)	Visit 5 (9 months)	Questionnaires (12,15,18 months)	Questionnaire (21 months)
Eligibility checks	✓	✓	✓						
Consent		✓							
MED test		✓							
Baseline characteristics (alternative timing)		✓	(✓)						
Digital images (alternative timing)		✓	(✓)				✓		
Training session (alternative timing)		✓	(✓)						
Supervised Treatment Session		✓	(✓)						
MED test results			✓						
Randomisation			✓						
Telephone support check				✓					
% repigmentation					✓	✓	✓		
Noticeability					✓	✓	✓	✓	✓
Onset of treatment response					✓	✓	✓		
Maintenance of treatment response								✓	✓
Quality of Life questionnaires		✓					✓		✓
Adverse reactions				✓	✓ & Diary	✓ & Diary	✓ & Diary		
Treatment usage & adherence				✓	✓ & Diary	✓ & Diary	✓ & Diary		
Health resource use		✓			✓ & Diary	✓ & Diary	✓ & Diary	✓	✓

TREATMENT REGIMEN

Participants will choose during the baseline / screening visit which patches of vitiligo (up to three) will be treated and assessed during the trial. Participants will be instructed to treat these three patches consistently throughout the trial. Nevertheless, participants will be able to treat as many of their vitiligo patches as they wish, as would occur in normal practice. This approach allows assessment of both person-specific outcomes (e.g. quality of life and time burden of treatment), as well as outcomes specific to individual patches of vitiligo.

Regimen for Topical Therapy- Mometasone Furoate 0.1% or Placebo

Topical therapy is to be applied once daily on a 'one week on, one week off' basis, for a period of 9 months. This discontinuous regimen has been defined in order to minimise the risk of adverse reactions, although the European Guidelines for the Management of Vitiligo state that there are currently no studies available on optimal duration of TCS therapy and on discontinuous applications that could be of help in improving the therapeutic index[18]. The SPC for mometasone furoate 0.1% recommends an application in children or on the face is limited to a duration of treatment of no more than 5 days. However, as vitiligo is known to respond at a slower rate to topical therapies than inflammatory skin conditions, it is clinically acceptable to recommend use of the topical corticosteroid for a longer period. The European Guidelines advise that in children and adults with limited extrafacial vitiligo, a potent steroid (such as mometasone fuorate 0.1%) should be used in a discontinuous treatment scheme, such as ‘15 days per month for 6 months with a strict assessment of response based on photographs’. The European Guidelines also state that newer class III TCS such as mometasone furoate are largely devoid of the side effects seen with other TCS, so the risk to participants is lower. There are no data available on the risk of side effects when TCS are applied to the face in the proposed discontinuous treatment scheme. However, participants' response to the ointment as well as side effects will be monitored even more closely than recommended in the European Guidelines (i.e. 3-monthly), based on photographs, and if upon any visit it is deemed unsafe for a participant to continue to use the topical corticosteroid for the remaining period of the trial, they will be instructed to stop. If the side effects resolve by the time of the next visit, they may re-start treatment.

Topical therapy should be applied at least two hours AFTER the hand-held light device is used, and not before, in order to avoid interaction of the NB-UVB light and topical corticosteroid.

For vitiligo around the eyes, participants should avoid application of the ointment directly to the eyelids and should avoid getting any ointment in the eye.

If a participant or parent/guardian is unwilling to use this treatment regimen at a particular body site (e.g. on the face of a child), the assessed patches of vitiligo chosen for that individual will be chosen on alternative body regions.

If a participant is concerned about any adverse reactions from the topical corticosteroid (e.g. skin thinning, striae atrophicae and telangiectasia, spread and worsening of untreated infection, contact dermatitis, perioral dermatitis, acne or worsening of acne or rosacea, hypertrichosis), they will be advised to contact the research team who will provide advice or arrange for a dermatological consultation (an unscheduled trial visit), depending on the severity and nature of the adverse reaction.
Dose reduction or suspension (temporary or permanent) of TCS use in response to side effects will be at the discretion of the treating dermatologist.

Regimen for NB-UVB Light or Dummy

Hand-held devices are held above the skin using a spacer to standardise the distance from the skin.

If the size of the patch to be treated is larger than head of the device, participants will be asked to move the lamp slowly over the area in circular movements.

Performing light therapy will be demonstrated in the training session and participants will receive advice on how to deal with possible side effects.

Participants will be supplied with the device, gloves and UV protective goggles, which must be worn at all times during each NB-UVB light treatment. If a participant is treating a patch of vitiligo on the eyelids, then goggles do not need to be worn during treatment; however, they will be instructed during device training to keep both eyes closed at all times when the light is switched on. In the case of children (or adults) who need help in administering treatment, the parent /carer administering the treatment will also be supplied with UV protective goggles and gloves. A digital timer is supplied with the hand held units.

Treatment will be self-administered at home, every other day (3 to 4 times per week), for a period of 9 months. The exposure time for each session will be increased incrementally in a pre-defined treatment schedule. These schedules will clearly detail the dose of light therapy they should be administering, and will provide details of how and when a dose should be increased or decreased. The participant will continue to increase the exposure time if she/he does not have any erythema reactions, until the maximum exposure time (MET) is reached. Once the MET is reached, the exposure time for each treated patch will remain the same (i.e. equal to the MET) for all subsequent treatment sessions.

Participants will maintain a record of their treatments in a treatment diary, which they will be required to complete. Should they develop any adverse device effects (other than mild erythema), they will be asked to contact a member of the trial team at the local hospital in order to confirm the next treatment time and dose or to arrange for a dermatological consultation (an unscheduled trial visit), depending on the severity and nature of the adverse reaction. Temporary or permanent suspension of light therapy will be at the discretion of the treating dermatologist.

Participants will be given detailed information in their trial handbooks to help them identify the grade of erythema, and determine the appropriate course of action for future light therapy treatment sessions:

-*Grade 1* Erythema is when the skin becomes slightly red or pink, and this change in colour does not last for more than 1 day following the treatment session. Grade 1 erythema requires going back one step on the light therapy treatment Schedule.

- *Grade 2* Erythema is when the skin is red (but not hot or very painful) for approximately 2 days following the treatment session. Grade 2 erythema requires skipping the next scheduled treatment session, and then going back one step on the light therapy treatment schedule for the next treatment.

-*Grade 3* erythema is redness of the skin which is both hot and painful. The burn can last for two or three days. Grade 3 erythema requires the participant to contact the local research team as soon as possible (or if out of hours, their GP, the out of hours on-call dermatologist at the local hospital or their local A&E department) for treatment. Under

advice of the local research team, it will be determined when it will be safe to resume light therapy treatments.

-*Grade 4* erythema is redness of the skin which is both hot and painful and also results in a blistering of the skin. The burn can last for four or five days. Grade 4 erythema requires the participant to contact the local research team as soon as possible (or if out of hours, their GP, the out of hours on-call dermatologist at the local hospital or their local A&E department) for treatment of the erythema. Under advice of the local research team, it will be determined when it will be safe to resume light therapy treatments.

Participants may stop using treatment during the 9 month treatment period if they feel that there has been a sufficient response (or if the vitiligo fails to respond to treatment). They may also restart treatment during this period (from the first dose schedule in the case of NB-UVB light) should the vitiligo return. The primary end point will be their opinion of the change in their target patch at 9 months irrespective of whether treatment was continuous, was stopped prior to 9 months or was stopped and restarted within the 9 month treatment period.

At 9 months, all participants will stop using their trial interventions and will enter the follow-up phase.

Missed Treatments or temporary stopping of treatment

If any applications of the topical therapy (topical corticosteroid / placebo) are missed, participants should re-start as soon as possible, keeping to the 'one week on, one week off' pattern of treatment as closely as possible.

If light therapy sessions are missed, other than for planned breaks due to erythema reaction (e.g. due to illness or being unable to administer treatment for some reason), then the following steps should be taken.

- 1 or 2 missed treatments: administer exposure time for the previous session (i.e. reduce time by one increment on the treatment schedule)
- 3 missed treatments: reduce time by two increments on the treatment schedule
- 4 or more missed treatments: participants must contact the research team for further advice regarding reduction of dose. If 4-6 treatments have been missed, the next dose should be around 50% of the last dose given (co-ordinating centre or research nurse will advise participant regarding what dose to administer)
- If more than 6 treatments are missed, the participants should re-start the treatment schedule from the beginning.

Concomitant and Rescue Medications and Treatments

Concomitant medications/treatment should be kept to a minimum during the study. However, if considered necessary for the participant's welfare, they may be used at the discretion of the treating physician according to the local standard of care. Participants will be given a trial id card detailing their potential treatments to show any treating physicians or pharmacists at the time of being prescribed medication or purchasing over the counter medication.

In order to prevent interactions with any potential photosensitive medications, participants will be instructed to inform the local research team of any changes in medication or new medications (over the counter or on prescription) before continuing with their light therapy treatments.

Some medications can occasionally cause photosensitivity (a rash in areas of skin exposed to light). The risk of these reactions is very low for NB-UVB light. Participants will be advised at the start of the trial that these reactions can sometimes occur, and that they should contact a member of the trial team if they develop any persistent rash that occurs during the treatment period.

All concomitant medications and treatments will be documented on the Case Report Form (CRF) (using generic name and trade name as appropriate) and also in the participant's medical records. These medications and treatments will be documented at baseline and at each subsequent visit during the treatment phase.

Since NB-UVB light is a form of radiation, participants should not allow themselves to be exposed to any other form of light therapy during the treatment phase of the trial. This includes any other kind of phototherapy (either at home or in hospital), intense pulsed light, laser treatment and sunbeds.

Compliance and Treatment Adherence

Compliance with the protocol will be monitored. This will include following up participants who have not completed questionnaires and/or attended for clinic visits. Any instances of unblinding of treatment allocation will be recorded.

Adherence with trial treatments will be recorded in the treatment diary (as an aide memoir) and information summarised during clinic visits.

Accountability for drugs & placebos

Detailed distribution records will be kept in a secure database held by NCTU for the central pharmacy, Mawdsleys. Mawdsleys will also use their own in house recording procedures. Information kept will include participant study number and initials, batch numbers of ointment tubes, expiry date and dose of ointment, device number of device sent and date of distribution.

Unused medication and devices will be returned to the recruiting site at the 9 month appointment. Local pharmacy will dispose of the unused ointment as per the local procedures, and the device will become the property of the local NHS Trust.

Management of study drug overdose

The risk of overdose of the topical corticosteroid is very low. Topical corticosteroid can be safely applied to the whole body in a single dose with minimal risk of adverse reactions. There is however a risk of adverse reactions following long-term use of topical corticosteroid to localised areas of skin (e.g. skin thinning, telangiectasia) and these will be monitored during follow-up visits (or in unscheduled trial visits, as necessary).

Management of any overdose of NB-UVB light (i.e. exposure to NB-UVB light for a longer time than scheduled) will depend on the degree of overdose and when it is discovered. In general, treatment should be sought as soon as the overdose is discovered, rather than waiting for a reaction to occur (usually about 24 hours after exposure). Early intervention with 2-3 days of a super potent topical corticosteroid is the standard treatment for accidental overdose of NB-UVB light.

The possibility of NB-UVB light overdose and what to do in such an event will be thoroughly covered in both the face to face training session and in the trial handbook, given to participants at the training session.

If a participant inadvertently administers an overdose of NB-UVB light, or if they experience a grade 3 or 4 erythema, they will be instructed to apply their trial ointment in liberal quantities to the exposed skin and to contact a medically-qualified professional immediately. They will be made aware that the burn will not appear straight away after the accidental overdose, but that urgent action is required as soon as the accidental exposure is discovered.

An urgent appointment will usually be made with the PI or one of their team at the site where the participant was recruited. However, since immediate medical advice is required, participants will be instructed to seek treatment from any local emergency service (this could be emergency on-call dermatology service, accident and emergency or their GP if the trial investigator is unavailable or if necessary by a member of the local dermatology on-call team).

Details of how to treat an accidental overdose will be included in the participant's trial handbook and on their study id card. Participants will be instructed to share this information with whoever treats them for their accidental overdose (as clinicians not familiar with the use of light therapy may not be aware of the treatment protocol for managing accidental exposure). Usual care for management of an accidental overdose of NB-UVB light is to apply topical clobetasol propionate 0.05% twice a day for 2 to 3 days. This will be prescribed by the treating clinician as per normal care.

Criteria for terminating trial

If severe adverse reactions associated with either of the interventions (topical corticosteroid or NB-UVB light) occur frequently, the study may be terminated on the advice of the Trial Steering Committee and / or the Data Monitoring Committee.

The sponsor (in collaboration with the TMG and TSC) may stop the trial or terminate one centre if new information becomes available causing major safety concerns, or if there are issues with trial conduct, or lack of recruitment.

Should the trial be terminated, the research data will not be destroyed.

STATISTICS

Methods

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. Further details about the statistical analyses will be provided in the Statistical Analysis Plan which will be finalised prior to completion of data collection, database lock and unblinding of the study.

Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages. Descriptive statistics of demographic and clinical measures will be used to examine balance between the randomised arms at baseline.

The primary approach to between-group comparisons will be to analyse participants according to the group to which they were allocated, regardless of treatment received, and without imputation of missing outcome data. Sensitivity analysis will be used to investigate the impact of missing primary outcome data.

All data will be analysed using Stata version 13 or later.

Sample size and justification

The research literature with which to inform our sample size is limited. However, based on evidence of previous trials of light therapy in combination with topical steroids ([45-47] and unpublished data from Amsterdam trial by Kroon et al) and of topical corticosteroid as monotherapy [48] we have calculated the sample size assuming a range of different treatment responses.

For this three-arm study, two comparisons are of primary interest: NB-UVB light alone versus topical corticosteroid alone, and NB-UVB light plus topical corticosteroid versus topical corticosteroid alone. Assuming that 15% of participants allocated to receive topical corticosteroid alone achieve treatment success, 372 participants are required to detect an absolute difference of 20%, with 2.5% two-sided alpha and 90% power. Assuming 15% non-collection of primary outcome data, an original sample size of 440 participants was set. Our choice of minimum clinically important difference between the groups has been informed by a survey of the clinical membership of the UK Dermatology Clinical Trials Network. This survey showed that clinicians were keen to see at least a 20% difference between the groups for it to be worth changing their practice to include the provision of hand-held light therapy. Light therapy is expensive both in terms of time and resource, and carries additional safety risks, so a substantial additional benefit would be required in order to change practice.

The calculation was performed using Stata version 13.

TCS + dummy UVB	UVB + placebo TCS	UVB + TCS	Total n	Total n with 15% loss to follow-up
10%	30%	30%	321	378
15%	35%	35%	372	438
20%	40%	40%	414	487
25%	45%	45%	447	526
30%	50%	50%	471	554

Due to uncertainty in the estimated proportion in the comparator arm (Group A) who will report treatment success on the primary outcome, provisions were laid out for the original sample size assumptions to be checked by the independent DMC after 18 months of recruitment. This check took place as planned and involved examination of retention at primary follow up by treatment arm, and of the observed primary outcome rate in the comparator arm only. This review resulted in a recommendation by the DMC to the TSC to increase the sample size by a further 76 participants in order to maintain 90% power to detect a risk difference of 20% between the topical corticosteroid arm and the other two arms. This recommendation was approved by the Trial Steering Committee, and the revised target sample size is therefore 516.

Assessment of efficacy

For the primary outcome, 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?") will be reported for each treatment group at 9 months from randomisation. Randomised groups will be compared using a generalised linear model for binary outcome adjusted by centre, site of vitiligo, and age. 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 in the proportion of participants achieving treatment success at 9 months along with 95% confidence interval and exact p-value. Sensitivity analyses will be conducted to (i) further adjust for any variables with marked imbalance at baseline, (ii) investigate the impact of missing primary outcome data, using simple and multiple imputation, and (iii) investigate the effects of treatment adherence. Planned sub-group analyses will include i) children versus adults, and ii) by body region of the target vitiligo patch. Further secondary analyses of the primary outcome will be defined in the statistical analysis plan prior to locking the trial database. These analyses will be conducted by inclusion of appropriate interaction terms in the regression model, and will be considered as exploratory.

Analyses investigating other follow up times, treatment success of patches on other body sites, and other secondary outcomes will be analysed by a similar approach, using appropriate regression modelling depending on outcome type.

Assessment of safety

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[32]. 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.

Cost-Effectiveness Analysis

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

i) active hand-held NB-UVB light compared to standard care (topical corticosteroids only),
ii) active hand-held NB-UVB with potent topical corticosteroids compared to standard care (topical corticosteroids only) using established methods

An incremental cost analysis will be conducted from an NHS perspective capturing the intervention resource use and other health resource use throughout the treatment and follow-up period (21 months in total). In addition to an NHS perspective, but presented separately, an estimate of out-of-pocket and time costs of treatment for participants and parents/guardians will be recorded. Intervention and wider health care costs will be estimated during the trial through participant dairies and CRFs. Resource use will be valued using

published unit costs or participant reported estimates for a common price year. Both costs and benefits will be discounted using recommended rates.

Both an incremental cost-effectiveness analysis using the trial primary outcome to estimate the incremental cost per successful treatment and cost-utility analysis estimating incremental cost per quality-adjusted life years (QALY) will be conducted. Utility will be measured at screening/baseline, 9 months and 21 months using the EQ-5D-5L[37-39] (for adults and children aged 11 years or over) and CHU-9D[39-42] (for children aged 5-17 years) questionnaires, which will be used to estimate the quality-adjusted life years over the study period using linear interpolation and area under the curve analysis with baseline adjustment[49]. In the base case a separate cost utility analyses will be presented for those aged 18 years and over using the EQ-5D-5L to estimate QALYs and for those aged under 18 years using the CHU-9D. The interventions will be ranked from least to most costly, dominated interventions (i.e. those that are more expensive and less effective) or those subject to extended dominance (i.e. less effective and have a higher Incremental Cost Effectiveness Ratio (ICER) will be excluded before re-calculating the ICERs which will be assessed in relation to a range of cost effectiveness thresholds (different levels of willingness to pay for health benefits). Decision uncertainty will be presented via Cost-Effectiveness, Acceptability Curves (CEACs) based on non-parametric bootstrapping of cost and effect pairs. This will provide robust trial evidence to inform decision makers about the likely cost-effectiveness of interventions for vitiligo in particular about whether NB-UVB light is more cost effective than topical corticosteroid alone and about whether combination treatments offer greater value for money than either treatment alone.

Procedures for missing, unused and spurious data

Every effort will be made within the trial to minimise the occurrence of missing data. For the primary outcome at week 36, participants failing to attend their scheduled clinic visit will be followed up either by telephone or post in order to minimise missing data for the primary outcome.

All missing data items will be tabulated by treatment arm and reasons given where possible. We will examine the plausibility that data are missing at random (MAR) and multiple imputation techniques will be used to handle missing values as appropriate.

Definition of populations analysed

Analysis will be according to intention-to-treat. The definition of the populations to be analysed will be clarified in the statistical analysis plan prior to closing of the trial dataset.

ADVERSE EVENTS

Definitions

An **adverse event (AE)** is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

For the purpose of this low risk study all adverse events and assessment of causality will be recorded by sites in the source data for all participants. If the local investigator feels there is a possible relationship with the interventions the adverse reactions will be captured and reported through the eCRF. Adverse events are only collected during the 9 month treatment phase (no post-treatment wash-out period is necessary as the treatments are not systemic and side effects will not occur after treatment use stops).

Common adverse reactions to the trial treatments are listed below, but are not limited to:

- atrophy, including thin 'paper money' skin,striae atrophicae ('stretch marks'), telangiectasia, bruising
- acneiform rash
- perioral dermatitis (when used around mouth)
- skin hypopigmentation (in darker skin types)
- spread or worsening of skin infections
- contact dermatitis at site of application
- worsening of acne or rosacea
- hypertrichosis (increased hair growth)
- erythema*
    - Grade 3 erythema (severe) – well defined symptomatic / painful erythema
    - Grade 4 erythema (very severe) – painful erythema, usually with bullae.
- blistering (without erythema)
- other new persistent rashes, (e.g. polymorphic light eruption, lupus etc).
- pruritus (itching)
- xerosis (skin dryness)
- *cold sores*

**Grade 1 and Grade 2 erythemas will be reported and recorded, but are not classified as AEs for the purpose of this trial as they will be treated as expected treatment effects of the light therapy treatments, as therapeutic doses of UVB will incur some minor erythema.*

Reference source: SmPC for Elocon (mometasone furoate 0.1%) ointment (Section 4.8) and the Phototherapy Training Manual written by the Phototherapy Unit at St Woolos Hospital, Newport (32).

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that leads to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A **Serious Adverse Event (SAE)** is any adverse event occurring following study mandated procedures, having received the treatment or placebo/dummy that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE's causal relationship to the study IMP is assessed by the PI at site as "possible", "probable", or "definite" is an Adverse Drug Reaction, and this assessment is and confirmed by the Chief Investigator

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately upon being made aware of any serious adverse event. All serious adverse events and serious adverse device effects will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Sponsor (or designee) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

The Sponsor will delegate the role of assessing adverse events to the CI (the designee).
All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

SUSAR

Suspected unexpected serious adverse reaction (SUSAR) A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the coordinating centre and the Chief Investigator (CI).

The CI will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP or device.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site.
- Shall inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required.

Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the CI.

The CI will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required.

Participant removal from the study due to adverse events

Any participant who experiences an adverse event (to IMP or device) may be removed from treatment at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Investigator Site File. A third copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial. A fourth copy will be sent by the site staff to the participant's GP.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to potential participants that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Detailed distribution records will be kept by Mawdsley Brookes and Company Ltd, who is in charge of distribution.

Unused ointment will be returned to the recruiting site at the 9 month appointment and a record will be made prior to destruction.

Device accountability

Detailed distribution records will be kept by the central pharmacy.

At the 9 month appointment, devices will be returned by the participant to the recruiting centre. The return of the devices will be recorded. Any participant who has not returned their device will be followed up by the site research staff and the Nottingham Clinical Trials Unit, to ensure the return of the device and the ongoing safety of the participant.

Electronic Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on eCRFs, digital photographs, other trial documents and the electronic database. The documents will also use their initials (of first and last names separated by a hyphen or a middle name initial when available). The participant's date of birth (dd/mmm/yyyy) will be recorded in the database.

The eCRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

Participant name, trial identification number, and contact details will also be logged onto the secure randomisation system based at the NCTU. These details will be shared with Mawdsley Brookes and Company Ltd for the sole purpose of sending out the intervention at randomisation (or sending of resupply of the IMP if needed), and also used by the trial management staff in order to send out study related questionnaires, correspondence and follow-ups, limited to the duration of the participant's participation in the trial. Participants may also optionally consent to their contact details being retained beyond the duration of their participation in the trial, in order to be updated about the outcomes of the research, or informed of future research.

The eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be completed and collected in line with GCP. The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms and current medical records. Parts of the eCRF may serve as its own source data. Sites must complete a source data location log which lists where source data can be found. This should be filed in the Investigator Site File and a copy provided to the trial management team at the coordinating centre. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The eCRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the Chief Investigator, Sponsor's designee, local monitoring teams and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be

limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Manager/Monitor, or where required, a nominated designee of the Sponsor, shall carry out monitoring in accordance with the trial monitoring plan.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Manager/Monitor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity in accordance with the trial monitoring plan.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (as defined in the monitoring plan and based on risk assessment for the trial) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

During the period of the trial, press releases will be issued from the Centre of Evidence Based Dermatology and/or the Nottingham Clinical Trials Unit at the University of Nottingham. No party will be entitled to submit any publicity material without prior approval from the co-ordinating centre.

Trial publications and conference presentations will be submitted to the NIHR HTA for approval prior to submission to the event organisers or the editors. All publications will acknowledge the support of the HTA in funding this trial. All participants will receive a copy of the trial results in the form of a participant newsletter. Neutral or negative results will not constitute a reasonable justification to delay publication.

USER AND PUBLIC INVOLVEMENT

This trial has been developed in response to a James Lind Alliance Priority Setting Partnership (PSP) that identified this as an important topic for further research for patients and clinicians. The PSP process was also used to identify the most important outcome measures for use in vitiligo trials, and these results have been used to guide our choice of outcomes. A patient with vitiligo has been actively involved in the trial development group (as well as the Cochrane systematic review and pilot trial), and is a co-applicant on the grant. Feedback from participants in our pilot trial has been used to inform the data collection tools, training materials and choice of devices to be used. An on-line survey of patients and clinicians to establish the most important outcomes to be measured in future clinical trials highlighted the importance of measuring acceptability of treatment response in addition to percentage repigmentation (24). We have therefore carried out work with people with vitiligo, using online surveys and discussion groups, to create a validated patient-rated outcome measure of treatment success, which we will use as our primary outcome measure in this trial.

STUDY FINANCES

Funding source

This study is funded by NIHR Health Technology Assessment - Ref 12/24/02.

Participant stipends and payments

Participants will not be paid to participate in the trial. As an inconvenience allowance, participants will be given a £10 high-street voucher for each clinic appointment attended. Small trial-branded gifts with a low monetary-value (torches, key rings, etc) will be given periodically throughout the trial at clinic appointments.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Jonathan Batchelor

Signature:

Date:

Deputy Chief Investigator: Kim Thomas

Signature:

Date:

Trial Statistician: Alan Montgomery

Signature:

Date:

Trial Pharmacist: Paula Blance

Signature:

Date:

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Appendix 1: Home Interventions and Light therapy for the treatment of vitiligo (HI-Light): mixed methods process evaluation within a randomised controlled trial

BACKGROUND AND RATIONALE

The HI-Light Vitiligo Trial has been funded by the HTA to assess the effectiveness of home narrow-band ultraviolet B light and topical corticosteroids for the treatment of patients with early and limited non-segmental vitiligo. Participants aged 5 years of age or over with active non-segmental vitiligo receive a standardised phototherapy treatment plan, with phototherapy (or dummy) to be administered at home three to four times per weeks. Participants are also given a potent topical corticosteroid (or placebo) to use once daily on alternate weeks (one week on, one week off). Both treatments are used for a period of 9 months.

A feasibility trial (Eleftheriadou et al 2014) of hand-held UVB for vitiligo found that 86% of participants (25 of 29) were judged as having good intervention adherence, but treatment duration was only 4 months and there was no combination therapy with topical corticosteroids.

If the trial is conducted in isolation, outcomes evaluations may leave important questions unanswered. A process evaluation can help to explain trial findings, explore how intervention delivery within the trial may differ from 'real world' delivery and identify issues important to the transferability of an effective intervention outside the trial (Moore et al 2014). This mixed methods process evaluation has been funded by the HTA to run alongside the main trial to investigate delivery of the interventions in the HI-Light Vitiligo trial.

A major potential barrier for implementing findings, if hand-held UVB and / or topical corticosteroids are shown to be effective, would be the implications for front-line practice. Dermatology services and primary care services are currently not routinely prescribing or advising hand-held UVB for any conditions, and potent topical corticosteroids are not widely used in this way for vitiligo (they are more often prescribed for use in a continuous manner for shorter periods, or milder topical corticosteroids may be prescribed in primary care). It is therefore important to explore the views of prescribers and commissioners who would be involved in delivering the interventions in order to identify how this service could be offered, if shown to be effective. We will also explore the views of patients and carers around their experience of using these treatments and availability of interventions and attitudes to paying for devices if they are shown to work. The views of those involved in delivering the trial will also be sought.

Aims

1. Facilitate interpretation of trial findings
2. Explore stakeholder perceptions of the feasibility and acceptability of the trial interventions in practice
3. Identify lessons for 'real world' implementation based on delivery of the interventions in the trial
4. Identify routes and barriers to implementation of findings

Objectives

1. To explore expectations and experiences of HI-Light trial participants in using the trial interventions
2. To explore the views of staff and managers at recruiting centres for the HI-Light trial (healthcare professionals, research nurses, support staff, and service managers) on the use of trial interventions including any variation in intervention delivery within the trial
3. To explore the perceptions of healthcare professionals and commissioners, staff at recruiting centres and trial participants on potential barriers and facilitators to the use of trial interventions in normal practice

METHODS

The process evaluation will use a combination of quantitative and qualitative methodology, with interviews of participants, trial site staff and health care professionals and commissioners alongside analyses of trial process variables. Interviews will be carried out by qualitative researchers who are members of the trial team but independent from the main RCT management.

Selection of Participants:

Trial Participant Interviews

Interviewees will be drawn from participants and parents/guardians who took part in the main HI-Light Vitiligo trial. Following completion of the 9 month treatment phase of the trial, participants and parentsguardians will receive a relevant information sheet about the optional interviews. This information will be given to trial participants by local site staff at the 9 month clinic visit. Invitation letters and information sheets may also be sent via email or post.

Shortly after they receive the information sheet about the optional interviews, participants or parent/guardians will receive a telephone or email follow-up from the qualitative researcher conducting the interviews to answer any questions they may have. If the participant or parent/guardian is interested in taking part, an interview time will be arranged.

To ensure a broad scope of views and experiences are included in the study, interviewees are needed to represent a range of demographics, including but not limited to, age, gender, and treatment group. The sampling will reflect themes emerging from the interviews as they progress. If any relevant demographic is underrepresented in the group of participants who put themselves forward for an interview after first contact, a purposive sample may be sought, with some participants being sent a second invitation letter and information sheet as a reminder.

Healthcare Professional Interviews

Staff at recruiting sites who have been involved in the trial, and staff responsible for delivery of dermatology clinical services (particularly phototherapy services) will be invited to be interviewed. Research leads at centres that expressed interest in taking part in the main trial, but did not become a trial site will also be approached to participate.

Prescribers and commissioners will be recruited through the CRN and other contacts.

Sample Size

Participant Interviews

We aim to recruit 10-15 of each age group participating in the HI-Light Trial:

- Parents /carers of children aged 5 to 11 years old
- Young people aged 12 to 17 and years and/or their parents/carers
- Adults 18 years and older.

Healthcare Professional Interviews

- Recruiting centres (n=16): health professionals and research staff from a representative sample of recruiting centres, plus centres that expressed interest in taking part in the main trial, but did not become a trial site.
- 15-20 prescribers and commissioners who are involved in provision of treatment for vitiligo

Eligibility

Trial Participant Interviews

Inclusion criteria

• Participant (or parent / guardian of child participant) in the HI-Light trial who has completed their 9-month visit, or who has stopped using trial treatments but have not withdrawn consent from trial participation.

• Able to give informed consent.

Exclusion criteria

• Unable to converse in English language

Healthcare Professional Interviews

Any healthcare professional who has a role in delivery of or decision making about treatment for patients with vitiligo and is willing to take part in the interview will be considered eligible.

Informed Consent

Participant Interviews

All participants will receive age appropriate participant or parent/carer information sheets in advance of the interview taking place, and will be given the opportunity to speak with the qualitative researcher to have any questions answered. Prior to the interview, participants will be sent a consent form to complete, by post, email or as an online link. Consent will be reconfirmed verbally at the beginning of the interview, and audio-recorded. If a participant does not return their consent form, the verbal consent will be corroborated by a second researcher and serve as sole proof of consent. Verbal consents will be logged and stored appropriately with trial files. For those participants who supply written consent, one copy of the signed consent form will be kept by the participant and one will be returned to the Investigator.

If a child (age 12-15) wishes to participate in the interview with their parent/carer, they will have an opportunity to give their assent.

Healthcare Professional Interviews

Verbal consent will be taken and recorded at the beginning of interviews with healthcare professionals, prescribers and commissioners.

Interviews

Participant Interviews

Data will be collected through interviews, conducted either face to face at the hospital or family home (depending on the participant's preference) or over the telephone. They will be audio-recorded to allow for later transcription. It is anticipated that interviews will last around 45 minutes. If a participant does not consent to audio-recording, detailed notes will be taken by the qualitative researcher.

Interviews will be largely one on one but participants will be welcome to invite a family member or a friend to be present during the interview if they wish. A parent will be present at the interviews of all children aged 12-15.

The qualitative researcher will conduct interviews following a semi-structured interview format. The participants/parents/carers/children will be asked for their opinion regarding their participation in the trial, how they found using the treatments including any concerns, and how they might like to see these made available to other patients. Open questions will seek to elicit participants' views from their own perspective, followed by prompts or more specific questions if necessary. New themes emerging during the interviews will also be explored.

Where participants would like to share their views but there is no suitable time found to conduct the interview either by phone or face to face but are otherwise willing to share their views, they will be offered an alternative of being sent questions by post or via an online survey.

Travel expenses related to attending interviews will be reimbursed and a £20 vouchers will be given for each interview in acknowledgement the interview participant's time.

The qualitative researcher may also consult relevant sections of the participant's main trial data or medical notes to help with the sampling and process evaluation data analysis.

Healthcare Professional Interviews

Face to face or telephone interviews will be carried out for the healthcare professional interviews. With healthcare professionals, we will cover their experiences of the participating in the trial, delivery of the training and how they might see this being rolled out in their hospital. For sites who wished to take part in the trial but were unable, we will ask about the barriers to setting up the trial at their site and perceived opinions on the trial treatments. With commissioners, we will explore what treatments they currently offer for vitiligo and their opinion on how these treatments and the training might be delivered. New themes emerging during the interviews will also be explored.

Data handling, Confidentiality and Safety

All interviews will be audio-recorded, with consent, and professionally transcribed verbatim. Where consent is not given to audio-record the interview, the qualitative researcher will take detailed notes whilst the conversation is ongoing. Transcripts will be checked against recordings and anonymised. Data handling will be facilitated through use of NVivo. Pseudonyms will be used in reporting the data and all data will be anonymised and stored securely on password protected computers. Audio recordings will be destroyed when t

Any contact details will be stored securely and separately from other data on a secure IT system.

The qualitative researcher conducting any interviews involving children will have had a DBS check. They will be conversant with the current national guidance in relation to

safeguarding children. Participants will be informed that data from interviews will only be used for the study. The only exception is that if any information disclosed to researchers may be of concern in relation to safeguarding (child protection) issues this will be reported to the child's health care team.

ANALYSES

Qualitative

Transcripts from interviews will be analysed using a Framework approach (Ritchie & Spencer 2002). Coding and analysis will be led by the qualitative researcher who will have collected the data, supported by the research team to bring different perspectives to the data and to ensure that the process of analysis is rigorous.

Qualitative data will be collected iteratively so that themes that emerge in early interviews can be further explored in later ones. Quantitative trial process data (such as recruitment rates, retention rates, and adherence) will be used to direct purposive sampling, for instance if participant adherence to interventions varies by recruiting centre.

Quantitative

Trial process variables will be analysed, for instance recruitment rates and withdrawals. Patterns will be sought for whether these differ by participant and site characteristics. Differences in sociodemographic characteristics between participants who did and did not adhere with the intervention will be examined, as will data on adverse effects collected as part of the trial.

Differences between sites that agreed to participate and those that did not will be examined; for instance whether social demographics, views of health professionals or service provision differ at these sites. Minutes of Trial Management meetings and teleconferences with sites will also be examined to capture any issues that arose in trial set-up or delivery.

Descriptive statistics will be used to present the trial process data with tests of association where appropriate.

We will ensure that quantitative and qualitative analyses build upon one another, with qualitative data seeking to explain quantitative findings, and quantitative data used to test hypotheses generated by qualitative data in line with MRC guidance (Moore et al 2014).

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Appendix 2:

MRC START in HI-Light:

What are the effects of a multimedia resource on recruitment?

An embedded, cluster randomised controlled trial

1. Background

In the UK, the NIHR vision sees 'more patients and health professionals participating in health research' [1]. Fundamental to health research is the testing of interventions through randomised controlled trials (RCTs). Achieving high participation in RCTs has traditionally been difficult. Published data show that a minority of RCTs recruit successfully [2,3]. Recruitment problems reduce the total recruited sample (limiting internal validity), and the proportion of eligible participants who are recruited (limiting external validity).

Clearly, there is a need to develop and test interventions to improve recruitment, and one method is to embed trials of recruitment interventions in ongoing (RCTs). Given the consensus among the research community concerning the challenge of recruitment, it is surprising that embedded trials of recruitment interventions are so rare. A recent Cochrane review identified 45 embedded studies in trials, nearly half of which looked at recruitment to hypothetical trials [4]. Recruitment for science is not underpinned by a science of recruitment.

The MRC START study is designed to develop the conceptual, methodological and logistical framework for embedded studies, and to assess their feasibility[5]. At the completion of MRC START, we will have rigorously tested two potential interventions for adoption in to routine practice, and provided the framework to make delivery of embedded recruitment RCTs a routine activity. This will assist the rapid development of recruitment to meet policy goals [6].

The HI-Light study is acting as a host trial to test an MRC START recruitment intervention. This protocol details the work that will be undertaken for MRC START in the HI-Light study.

2. The intervention – Multimedia resource (MMI)

At present most patient information about trial participation is given in written form, but this does not necessarily represent the best way to communicate with patients about taking part in a trial.
Multimedia interventions may offer a useful strategy to improve communication about trial participation and so facilitate greater trial accrual and retention rates. The diverse methods of information delivery possible via multimedia platforms provide alternative channels for health communication, in particular the Internet provides an opportunity for self-directed and tailored learning and for alternate language versions of information [50,51]. However the impact of multimedia information on patient identified barriers and motivators to clinical trial participation has not been rigorously explored.

The MRC START team has developed a multimedia resource in conjunction with www.healthtalkonline.org (the award winning website of the DIPEx charity which allows patients and the public to share peoples experiences of over 60 health related conditions and illnesses).

The structure and content of the multimedia resource have been developed based on:

- a review of research on patient decision making conducted by the research team
- a workshop run at the PCRN national conference (November 2012), led by a clinician with considerable PCRN expertise and attended by PCRN research staff
- design input and feedback from the Patient and Public Involvement representatives from the University of Manchester PRIMER group (http://www.population-health.manchester.ac.uk/primer/) and
- expertise from within the MRC START project team which includes clinicians, psychologists and experts in clinical trials.

The website consists of three sections:

- A home page identifying the host trial and offering potential participants the options of more information on medical research in general or finding out more about their trial.
- Generic pages on medical research consisting of edited video clips and infographics. The video clips, all from healthtalkonline, [www.healthtalkonline.org] are of patients talking about their experiences of medical research. The clips were selected and edited by patient and public involvement representatives from PRIMER working directly with a GP from healthtalkonline. They reflect the key concerns or issues raised by patients when talking about participation in research in the healthtalkonline interviews. The infographics on these pages were developed for the website based on material provided by the research team and the PRIMER representatives who then commented extensively on drafts to acheive the finished product.
- Study specific pages. The structure of the study specific pages was developed by the MRC START team and PRIMER representatives. This section of the website is designed to host video content and text specific to each host trial. For the HI-Light trial, subtitles of video clips will be available in Hindi, Urdu and Welsh, these being the three most prevalent non-English languages amongst the study population.

It would be useful to know if the START MMI in addition to the existing participant information sheet impacts on rate of recruitment, in comparison with standard host trial recruitment procedures. An embedded randomised controlled trial would be the best approach to evaluate its effects. The HI-Light study is one of six RCTs that will explore this as part of the wider MRC START research programme.

3. Host trial study details

The HI-Light study is a multi-centre 3-arm, parallel group, placebo-controlled, double-blind, randomised trial. HI-Light compares the effectiveness of topical corticosteroids versus (i) home-based NB-UVB light, and (ii) the combination of topical corticosteroids and home-based NB-UVB light therapy for the management of early and limited vitiligo in adults and children.

HI-Light will include approximately 10 - 12 UK centres. At each centre, potential participants will be identified from secondary care, primary care (approximately 100 GP surgeries in total) and through local advertising. Randomisation will take place in secondary care. 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).

Only participants recruited through primary care will be included in the embedded START study as randomisation will be at the unit of the GP surgery (cluster randomised), rather than by individual randomisation. Participants recruited to the HI-Light trial through secondary

care and through direct advertising will not be included in the embedded study, but directed to the MRC START trial website.

4. MRC START in HI-Light Research Objectives

- To establish if the number of patients recruited in to the HI-Light study from primary care is improved by access to the START MMI, compared to the standard HI-Light recruitment procedures.
- To explore whether access to and use of the MMI improves retention in the HI-Light study

5. Method

5.1 MRC START in HI-Light Design

Population: Eligible patients approached via participating practices in primary care
Intervention: Potential participants in primary care will receive a letter from their GP, a patient information leaflet and access to the START MMI
Comparator: Potential participants in primary care will receive a letter from their GP, a patient information leaflet and access to the standard HI-Light trial website
Outcome: the proportion of patients recruited to the HI-Light trial. Secondary outcomes will be: the proportion of patients in each intervention group who agree to participate in the HI-Light trial (where this differs from the number actually recruited, due to e.g. screening or other criteria); the proportion of patients retained in the study; and, the numbers of people from black and ethnic minority groups who respond positively to the invitation and are randomised into the HI-Light trial

The embedded trial will use a cluster randomised controlled design. Those who are identified as potential participants in HI-Light will be randomly allocated at the practice level to one of two participant information conditions:

- the intervention group will be sent the standard study participant information. In addition they will receive access to the MRC START MMI via a web link and QR code;
- the control group will be sent the standard study participant information and be given access to the standard HI-Light study website (which does not have video content to aid recruitment).

5.2 Inclusion/ exclusion criteria

The START embedded trial will include all patients in primary care identified as potentially eligible for HI-Light and contacted via their GP: there are no additional inclusion or exclusion criteria.

5.3 Recruitment and Randomisation

Potential participants in the HI-Light study drawn from primary care will be identified by searching patient lists at participating practices. All potentially eligible patients will receive a letter from their GP introducing the HI-Light study, a participant information leaflet and access to either the START MMI or the standard study website. Website details will be provided on the GP letter and participant information sheet. Patients responding positively to the letter will then undergo screening to confirm eligibility before being randomised into the HI-Light trial.

Allocation of practices to the embedded trial will be minimised by recruitment centre and practice size retaining a random element, and implemented using a secure, online randomisation system created and maintained by Nottingham Clinical Trials Unit, thereby ensuring allocation concealment.

The HI-Light team will record the following data for each practice and patient:

- numbers invited to participate in the research
- recruitment status
- expressions of interest not recruited & reason (eg screening outcomes)
- randomised allocation (START embedded trial)
- patient Screening ID number
- demographic data if available

At the screening visit the HI-Light team will also collect information on the sources of trial information potential participants have seen. We will collect information during screening that allows us to describe potential contamination of the control group by asking: How did you hear about the HI-LIGHT Trial? Response options: letter from GP, letter from a hospital doctor (dermatologist), through a patient support group, through general advertising (e.g. radio, TV, poster, advert), other. If they tick both GP letter plus one of the other options, then they will be classed as potentially contaminated.

Additional information will be collected during the invitation & screening process as follows:

- Have you sought treatment advice about your vitiligo from any of the following: GP; hospital doctor; other?
- Ethnic group.
- Name and address of GP (so that we can be clear as to randomised allocation for individual patients within each cluster)

5.4 Intervention

The START MMI resource consists of three sections:

1. a home page introducing the HI-Light study and offering potential participants links to:

2. generic pages on taking part in medical research (as described in section 2), and

3. study specific pages providing information about the HI-Light trial. The HI-Light trial team has already produced two patient videos which will form part of the study specific content. The HI-Light team will work with the MRC START team to produce further content for this section. The digital content in the study specific pages will be offered in alternate languages with subtitles provided in Hindi, Urdu and Welsh as these were the three most prevalent languages identified from the potential participant population.

Currently the blank development site can be viewed at:

http://mrcstart.reasondigital.com/blank-template/

5.5 Outcome measures

The primary outcome will be the proportion of patients recruited to the HI-Light trial. The HI-Light trial team will keep a record of all patients who were identified as potential participants and which START recruitment intervention group they were in.

Secondary outcomes will be:

- the proportion of patients in each intervention group who agree to participate in the HI-Light trial (where this differs from the number actually recruited, due to e.g. screening or other criteria);

- the proportion of recruited patients who are retained to the nine month primary outcome end point of the HI-Light study period.
- The number of people from black and ethnic minority groups who respond positively to the invitation and are randomised into the HI-Light trial

Additionally we will monitor the use of alternate language versions of the intervention website

6. Statistical considerations

6.1 Sample size

MRC START in HI-Light is a cluster randomised controlled trial being conducted in primary care practices in upto 12 study centres. The number of practices participating in the study will depend on overall recruitment to the HI-Light trial, including from other sources, but will likely be approximately 10 practices per centre. Randomisation is at the practice level and approximately 30 invitations will be sent out per practice. Although there are presently no good data on ICCs for response to invitations, we have assumed a conservative ICC of 0.05 consistent with a wide range of other primary-care based outcomes, giving a design effect [1+(m-1)*ICC] of 2.45. Pilot data suggest that up to 40% of potential participants invited in the control arm will be randomised, although in the main HI-Light trial it may be less than this as both light therapy and topical corticosteroids are being tested[9]. With 48 practices and 1440 invitations sent to potential participants, the study has 80% power (5% two-sided alpha) to detect absolute differences in recruitment in the range 8%-11% if the proportion recruited in the control arm is in the range 10%-50%. With 100 participating practices, the detectable effect decreases to 5%-8%.

6.2 Data transfer and storage

Anonymised data from the HI-Light trial will be sent to the MRC START team in accordance with University of Nottingham and University of Manchester standard data sharing procedures. The University of Manchester has strict guidelines for data storage, access to study data and adherence to the principles of data protection (including the Data Protection Act 1998). The link to relevant information is:
http://www.staffnet.manchester.ac.uk/services/records-management/data-protection/data-protection-guidance/
University of Nottingham guidelines can be found at:
…http://www.nottingham.ac.uk/governance/records-and-information-management/data-protection/data-protection-policy.aspx
Datasets will be sent from the HI-Light trial team to the MRC START study team in electronic format (the University of Manchester can translate datasets in various formats through Stat Transfer). In addition, the HI-Light team will provide written details of the coding of variables in the dataset to allow consistent analysis. The dataset will be anonymised by the HI-Light team before transfer to the University of Manchester, removing all identifiable patient information such as names and addresses. Data may be encrypted before transmission to ensure security.

Data storage

Data from the HI-Light team will be transferred to a database combining results from all host trials on a secure server at the Centre for Primary Care, University of Manchester. All data received will be treated in the strictest confidence. Analysis of the data will take place by Professor Peter Bower and Professor Sandra Eldridge. Professor Bower will act as custodian for the combined dataset. The combined dataset will be stored by the University of Manchester in a secure location. Data from individual datasets will remain the property of MRC START host trial teams.

Environment

The NIHR School for Primary Care Research (http://www.haps.bham.ac.uk/primarycare/nspcr/index.shtml) comprises the leading academic centres for primary care research in England, with a focus on research to improve everyday practice in primary care. The MRC START research project is led by the Centre for Primary Care, Institute of Population Health, the University of Manchester (http://www.population-health.manchester.ac.uk/research/primarycare/)

The proportions of patients who express an interest in participating, attend screening and are randomised in to the main trial will be calculated for the two START recruitment intervention groups. The differences between the two proportions at each point will be calculated along with the corresponding 95% confidence intervals. The number of participants who were classed as being potentially contaminated will be presented descriptively.

Results from this trial will ultimately be combined in a meta-analysis with response rate data from other host trials participating in the MRC START programme and included in the Cochrane systematic review of recruitment interventions [4].

7. Ethical issues

NRES approval will be sought to conduct the embedded study, using the recruitment method described above.

MRC START has already received the following ethical approvals:

- full ethical approval (REC Reference 11/YH/0271) from NRES Committee Yorkshire and the Humber – South Yorkshire,
- a substantial amendment (covering the generic content in the MMI): REC Reference 11/YH/0271 Substantial amendment 2, 31/10/13), and
- a substantial amendment giving approval for the use of START interventions in trials with children and young people: REC Reference 11/YH/0271 Substantial amendment 3, 29/05/14) .

Patients will not have the opportunity to give informed consent to enter into the embedded recruitment study. This has been approved by NRES Committee Yorkshire and the Humber – South Yorkshire (REC Reference 11/YH/0271) on the basis that the embedded study is not withholding information – but is simply a supplementary form of presentation.

The embedded study (MRC START in HI-Light) will be registered by the HI-Light study team as a sub-study on ISRCTN.

8. Financial and Insurance Issues

The multimedia resource intervention for the embedded trial is funded as part of MRC START which is sponsored by the University of Manchester. It forms a sub-study to the HI-Light trial, which is sponsored by the University of Nottingham. Normal NHS and University of Nottingham indemnity procedures will apply.

9. Project Timetable

Date	Action
January 2015	Documentation for the embedded study agreed & signed off
February 2015	Submission to REC of application for substantive amendment
January 2015	Discuss/approve scripts with host trial and plan process of filming bespoke content with external digital media company
January 2015	On-site filming of bespoke content
May 2015	Recruitment to the embedded trial anticipated
October 2016	Recruitment to the embedded trial ends
January 2017	Data cleaning and submission of data set to MRC START team
December 2017	Collation of results and analysis, begin write up of trial level paper

10. Dissemination of research

The results of this embedded sub-study will be published in a peer-reviewed journal to further improve evidence base regarding effective recruitment strategies in trials. This publication will be led by the HI-Light study team – the START team will provide a template to assist in the drafting of an individual paper. It is anticipated that findings will also be included in the Cochrane review of trial recruitment interventions. In addition the data will be included in a meta-analysis of all studies recruited to the MRC START programme led by the MRC START team. Dissemination of research findings will be conducted in line with standard authorship arrangements.

11. References

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