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Article type : Original Article

Randomised controlled trial of topical corticosteroid and home-based narrowband UVB for active and limited vitiligo – results of the HI-Light Vitiligo trial

Short title: Home-based narrowband UVB and topical steroid for vitiligo

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Trial registration: ISRCTN17160087. 8th Jan 2015

Funding: This study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference 12/24/02). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Support for this trial was provided through Nottingham Clinical Trials Unit, the UK Dermatology Clinical Trials Network and the NIHR Clinical Research Network.

This paper represents a summary of the trial results. A full and detailed trial report will be published within the NIHR Journal and copyright retained by the Crown.

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Competing Interests:

All authors' organisations received financial support from the trial funder in order to deliver the submitted work; no authors received any additional support from any organisation for the submitted work; no authors reported financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no authors reported other relationships or activities that could appear to have influenced the submitted work. J Ingram is Editor-in-Chief of the BJD but had no role in the publisher's review of the submitted work.

What's already known about this topic?

- Vitiligo is a common condition, and can have a considerable psychological impact
- Topical corticosteroids (TCS) are standard care for vitiligo. Narrowband UVB (NB-UVB) is a widely used treatment, but it is usually only available as full-body treatment, delivered in secondary care
- Evidence for the use of hand-held NB-UVB in combination with topical corticosteroid (TCS) is very limited

What does this study add?

- For people with localised non-segmental vitiligo, combination therapy with NB-UVB light and potent TCS (mometasone furoate 0.1% ointment) is likely to result in improved treatment response compared to potent TCS alone but was only successful in around a quarter of participants.
- Both treatments are relatively safe and well tolerated when used over a period of 9 months.

- Treatment effects start to be lost soon after cessation of treatment, so ways of maintaining treatment response once treatment is stopped need further investigation

Summary

Background: Evidence for the effectiveness of vitiligo treatments is limited.

Objectives: To determine effectiveness of (a) hand-held narrowband-UVB (NB-UVB) and (b) combination of potent topical corticosteroid (TCS) and NB-UVB compared to TCS, for localised vitiligo.

Methods: Pragmatic, 3-arm, placebo-controlled RCT (9 months' treatment; 12 months' follow-up). Adults and children, recruited from secondary care and community, aged ≥5 years with active vitiligo affecting <10% of skin, were randomised 1:1:1 to receive: TCS (mometasone furoate 0.1% ointment + dummy NB-UVB); NB-UVB (NB-UVB + placebo TCS); or combination (TCS + NB-UVB). TCS applied once daily on alternating weeks; NB-UVB administered alternate days in escalating doses, adjusted for erythema.

Primary outcome: treatment success at 9 months at target patch assessed using participant-reported Vitiligo Noticeability Scale, with multiple imputation for missing data.

Results: 517 participants were randomised: TCS (n=173), NB-UVB (n = 169), combination (n=175). Primary outcome data were available for 370 (72%) participants. Target patch treatment success was 17% (TCS), 22% (NB-UVB) and 27% (combination). Combination treatment was superior to TCS: adjusted between group difference 10.9% (95% CI 1.0% to 20.9%; p= 0.032; NNT=10). NB-UVB alone was not superior to TCS: adjusted between group difference 5.2% (95% CI -4.4% to 14.9%; p= 0.290; NNT=19).

Participants using interventions >75% expected were more likely to achieve treatment success, but effects were lost once treatment stopped. Localised grade 3 or 4 erythema was reported in 62 (12%) participants (including 3 with dummy light). Skin thinning was reported in 13 (2.5%) participants (including 1 with placebo ointment).

Conclusion: Combination treatment with home-based hand-held NB-UVB plus TCS is likely to be superior to TCS alone for treatment of localised vitiligo. Combination treatment was relatively safe and well tolerated but was only successful in around a quarter of participants.

Trial registration: ISRCTN17160087. 8th Jan 2015

Introduction

Vitiligo causes loss of skin pigmentation, mainly due to automimmune destruction of melanocytes, [1-7]. It affects up to 2% of the world's population and age of onset is usually between 10 and 30 years[8-13]. Vitiligo has an impact on quality of life, especially if it occurs on visible sites, such as the face and hands[14-16]. It can lead to depression and anxiety, low self-esteem and social isolation[16-19].

Current clinical guidelines [20] recommend topical corticosteroids, topical tacrolimus, narrowband ultraviolet B (NB-UVB) and combination therapies for vitiligo. There are few well-designed randomised controlled trials (RCTs) assessing NB-UVB treatment for vitiligo[21].

Many people with vitiligo experience frustration in accessing treatment [22-24]. NB-UVB is usually reserved for people with extensive vitiligo and delivered in secondary care using full-body units, requiring regular hospital attendance [22]. Limited vitiligo can be treated with hand-held NB-UVB devices[25], but studies assessing these have been retrospective, or too small to inform clinical practice[26,27]. Using a hand-held NB-UVB device reduces the need for hospital visits and avoids exposure of unaffected skin to NB-UVB. Clinical studies have also suggested that treating vitiligo in its early stages is more likely to be beneficial than treating longstanding vitiligo [27,28].

We report the results of the **H**ome **I**nterventions and **Light** therapy for the treatment of Vitiligo Trial, which evaluated the comparative safety and effectiveness of potent TCS and hand-held NB-UVB for the management of active limited vitiligo in adults and children.

Methods

The trial protocol has been published previously[29,30] No changes were made to eligibility criteria or outcome measures after trial commencement. The study was approved by the Health Research Authority East Midlands (Derby) Research Ethics Committee (14/EM/1173) and the MHRA (EudraCT 2014-003473-42). Participants or their parents/carers gave written informed consent. The trial was informed by a pilot trial[31], and

registered prior to start of recruitment (ISRCTN 17160087; 8 January 2015). A full trial report is available through the NIHR Journal series.[32]

Study design and setting

A multicentre, three-arm, parallel group, pragmatic, placebo-controlled RCT, with nested health economics and process evaluation studies (reported separately).

Trial interventions were delivered in secondary care across 16 UK hospitals. Participants were identified through secondary care dermatology clinics, general practice mailouts, and by self-referral.

Participants were enrolled for up to 21 months (9 months' treatment; 12 months' follow-up) and attended hospital clinics on two consecutive days at baseline for recruitment and training, and then at 3, 6 and 9 months to assess outcomes. Follow-up thereafter was by 3-monthly questionnaires, by post or email.

Objectives:

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

Objectives 3 and 4 are reported elsewhere[30]

Participants

Participants were aged >5 years, with non-segmental vitiligo limited to approximately 10% or less of body surface area, and at least one vitiligo patch that had been active in the last 12 months (reported by the participant, or parent / carer). Full eligibility criteria are listed in the protocol[29].

Interventions

All participants received a NB-UVB light unit (active or dummy; used on alternate days) and topical corticosteroid (mometasone furoate 0.1% ointment (Elocon®, Merck, Sharp and Dohme) or vehicle (placebo), applied daily on alternate weeks. Any device found to have an output that was ±20% of the expected mean output, or a dummy device testing positive for any NB-UVB emission, was returned to the manufacturer. Treatments were continued for up to 9 months, and concomitant medications were logged. Further details of the interventions are provided in the protocol and full trial report[29,32].
Dummy devices were identical to active devices but used special covers that blocked transmission of NB-UVB. Placebo ointment was identical to active ointment.

Participants selected up to three patches of vitiligo for assessment; one on each of three anatomical regions (head and neck; hands and feet; and rest of body). One patch was selected as the target for primary outcome assessment and was reported as active (new or changed) within the last 12 months.

Outcomes

Outcomes covered core outcome domains for vitiligo[33,34].

Primary outcome

Participant-reported treatment success at the target patch of vitiligo after 9 months' treatment. Measured using the Vitiligo Noticeability Scale (VNS)[35,36] , with treatment success defined as 'a lot less noticeable' or 'no longer noticeable' compared with before treatment. Participants used digital images of the target patch before treatment to help inform their assessment.

Secondary outcomes

a) blinded assessment of treatment success (VNS) at the target patch assessed by a panel of three people with vitiligo, using digital images;

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

c) *onset of treatment response at the target patch:* assessed by investigators;

d) *percentage repigmentation*: at the target patch at 9 months, using blinded clinician assessment of digital images (0-24%, 25-49%, 50-74%, 75-100%). Investigator assessments were used if images at 9 months were unavailable;

e) *quality of life:* at baseline, end of treatment (9 months) and end of follow-up (21 months). Disease-specific quality of life (VitiQOL, Skindex 29) and generic quality of life (EQ-5D-5L) instruments were completed by adults aged >18 years. Children 5 to 17 years completed the CHU 9D (generic) and children aged >11 years also completed the EQ-5D-5L (generic);

f) *maintenance of treatment response*: assessed by participants for the target patch at 12, 15, 18 and 21 months;

g) *safety*: adverse device effects, and adverse reactions during treatment phase;

h) *time burden of treatment*: time per session for active NB-UVB treatment and participant-reported treatment burden for active TCS and NB-UVB treatments at 3, 6 and 9 months;

Adherence with treatments was recorded using treatment diaries and collated at 3-monthly clinic visits.

Randomisation and blinding of allocation and outcome assessment

Participants were randomised 1:1:1 to receive topical corticosteroid plus dummy NB-UVB (TCS group); vehicle ointment plus NB-UVB (NB-UVB group); or topical corticosteroid ointment plus NB-UVB (combination group). Allocation was minimised by recruiting centre, body region of target patch and age, weighted towards minimising the imbalance in trial arms with probability 0.8. The randomisation sequence was accessed by staff at the recruiting hospital, using a secure web server created and maintained by the Nottingham Clinical Trials Unit (NCTU) to ensure concealment.

A central pharmacy (Mawdsleys, Doncaster, UK) distributed interventions. The pharmacy was notified of the allocation for randomised participants via the web-based system and trial treatments were sent directly to participants' homes.

Only the NCTU programmer, pharmacy staff and the NCTU Quality Assurance staff had access to treatment allocations.

Additional blinded outcome assessments were performed by a panel of three people with vitiligo (for the primary analysis) and a clinician for the secondary outcome of % repigmentation, using digital images taken at baseline and at 9 months.

Statistical methods

Sample size

Assuming that 15% of participants allocated to receive topical corticosteroid would achieve treatment success[37], 372 participants were required to detect a clinically significant absolute difference between groups of 20%, with 2.5% two-sided alpha and 90% power. Allowing for up to 15% non-collection of primary outcome data at 9 months, the target sample size was 440 participants. A planned sample size review by the Data Monitoring Committee after 18 months of recruitment resulted in a recommended increase in sample size to 516 participants.

Analysis

All analyses were pre-specified in a statistical analysis plan, which was finalised prior to database lock[29] . Amendments to the analysis plan compared to the protocol are summarised (Supplementary Table 1).

The primary analysis included all participants, regardless of adherence, and with multiple imputation of missing outcome data. Analyses estimates were obtained from 30 multiply imputed datasets by applying combination rules developed by Rubin.[38] Prior to primary analysis, baseline characteristics were summarised by treatment arms and the availability of primary outcome at 9 months, in order to check the missing at random assumption of multiple imputation.

For the primary outcome, the number and percentage of participants achieving 'treatment success' was reported for each treatment group at 9 months. Randomised groups were compared using a mixed effects model for binary outcome adjusted by minimisation variables. The primary effectiveness parameter for the two comparisons of NB-UVB alone and combination treatment each versus TCS alone was the difference in the proportion of participants achieving treatment success at 9 months, presented with 95% CI and p values. By default, risk differences are reported, because these estimates are more clinically intuitive for binary outcomes. However, where models estimating risk difference did not converge, odds ratios are reported instead of risk differences.

Sensitivity analyses were conducted to (i) adjust for any variables with imbalance at baseline, (ii) repeat primary analysis based on participants whose primary outcome was available at 9 months and (iii) investigate the effects of treatment adherence. Complier Average Causal Effect (CACE) analysis[39] was conducted where taking >=75% of expected treatments was considered a complier. Planned subgroup analyses were (i) children versus adults; (ii) by body region of the target vitiligo patch; (iii) activity of target patch (hypomelanotic patch: definitely/maybe versus no); (iv) >= 4 years duration of vitiligo versus <4 years. These analyses were conducted by inclusion of appropriate interaction terms in the regression model and were exploratory.

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

An additional post-hoc subgroup analysis explored the impact of skin type (types I to III versus types IV to VI).

Patient and public involvement

People with vitiligo were involved in all aspects of the trial including prioritisation of the research questions, study design, oversight, conduct and interpretation of results[32].

Results:

Recruitment and participant characteristics

Recruitment was from 3rd July 2015 to 1st September 2017 with 517 participants randomised (398 adults, 119 children). Primary outcome data were available for 370 (72%) participants (Figure 1). Baseline characteristics were well balanced across treatment groups (Table 1).

Adherence

Median percentage of NB-UVB treatment days (actual/allocated) was 81% for TCS, 77% for NB-UVB and 74% for combination groups, and for ointment 79% for TCS, 83% for NB-UVB and 77% for combination. Just under half of participants used the treatments for over 75% of the expected duration (Supplementary Table 2). Assuming 100% adherence, and a participant with a skin type requiring dose escalation to the maximum dose in the treatment schedule, we estimate the maximum possible total dose of NB-UVB received over the 9-month treatment period to be 4mW/cm^2 x 822sec x 135 treatment sessions = 443.9mJ/cm^2.

In addition to written and online video training[40], participants received face-to-face training (mean 70 minutes), prior to using the treatments at home. For participants using active light devices, the median time taken to administer the treatment was approximately 20 minutes, including time for set-up, administering the light, and documenting timings and side effects in the treatment diary.

Difficulties in using the treatments are summarised (Supplementary Table 2). Burden of treatment was identified as an issue by 42/142 (30%) in the TCS group, 38/140 (27%) in the NB-UVB group and 36/149 (24%) in the combination group, although interpretation is difficult as all three groups used both treatments throughout (either active or dummy/placebo). Overall, NB-UVB treatment was reported to be more burdensome than treatment with TCS. Burden of treatment and side effects were the most commonly cited difficulties for both groups and were common reasons for discontinuation of treatment, along with lack of treatment response.

Blinding

At the 9-month visit, investigators reported possible unblinding for 21%, 28% and 27% of participants in the TCS, NB-UVB and combination groups respectively. More participants reported possible unblinding (39%, 55% and 44% in the TCS, NB-UVB and combination groups respectively), supporting the need for confirmation of the primary outcome using blinded outcome assessment.

Primary outcome

The proportion of participants who reported treatment success (a lot less noticeable or no longer noticeable) at 9 months was 20/119 (17%) for TCS, 27/123 (22%) for NB-UVB and 34/128 (27%) for combination treatment.

Combination treatment was superior to TCS: adjusted between group difference 10.9% (95% CI 1.0% to 20.9%; p= 0.032; NNT=10). NB-UVB alone was not superior to TCS: adjusted between group difference 5.2% (95% CI -4.4% to 14.9%; p= 0.290; NNT=19). (Table 2).

The proportion of participants achieving treatment success at 3, 6 and 9 months is shown in Supplementary Figure 1.

All sensitivity analyses were consistent with the primary analysis. Treatment effects were largest amongst participants who adhered to the interventions more than 75% of the time (Supplementary Figure 2).

There was no evidence that any of the treatments were more effective than others for any of the pre-defined sub-groups (Supplementary Table 3). Post-hoc exploration of treatment response by skin type (types I to III versus types IV to VI) also found no differences between the groups (Supplementary Table 3).

Secondary outcomes

Treatment success using digital images, assessed by people with vitiligo who did not participate in the trial, was consistent with the primary analysis but suggested greater treatment effects compared to trial participants' VNS assessments (Table 3).

Participant-reported treatment success at 9 months (all assessed patches) was lower for patches on the hands and feet than other body regions. However, the relative effectiveness of the three treatment groups remained similar in different body regions (Supplementary Figure 3, Supplementary Table 4).

Most participants had onset of treatment response by 3 months, defined as the target patch having improved or stayed the same (Supplementary Figure 4), with 40% in TCS, 61% in NB-UVB and 60% in combination group showing *improvement* in their vitiligo (that is, more than stopped spreading).

Treatment success defined as ≥75% repigmentation supported the finding that combination treatment was superior to TCS alone, but NB-UVB alone was not superior to TCS: 4 (3%) for TCS, 9 (8%) for NB-UVB and 18 (15%) for combination. Adjusted odds ratio 4.62 (95% CI 1.50 to 14.24) for combination compared with TCS, and 2.22 (95% CI 0.66 to 7.51) for NB-UVB compared with TCS Table 4.

Long-term follow-up

The percentage of participants followed up at 12,15,18 and 21 months after randomisation were 56%, 52%, 47% and 43% respectively. VNS scores throughout the 21-month study period are shown in Supplementary Figure 1. During the follow-up phase, over 40% of participants reported loss of treatment response by 21 months for all groups (Supplementary table 5).

Both generic and vitiligo-specific quality of life scores were similar at follow up across the treatment groups (Supplementary Table 6).

Safety

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

Details of adverse events of particular interest (grades 3 or 4 erythema and skin thinning) are shown in Table 5. Grade 3 and 4 erythemas constituted the majority of adverse events in the NB-UVB and combination groups, and these erythemas accounted for the higher overall adverse event rates in these groups. Fewer adverse events were reported in children than in adults.

Discussion

Main Findings:

The HI-Light trial was a large, pragmatic trial of home interventions for people with active, limited vitiligo. Combination treatment with hand-held NB-UVB and potent TCS is likely to be superior to potent TCS alone (NNT 10), although the confidence intervals around this result were quite wide. We did not find clear evidence that hand-held NB-UVB monotherapy was better than TCS monotherapy. Results for percentage repigmentation (the most commonly used outcome in vitiligo trials[41]) were consistent with the participant-reported primary outcome using the Vitiligo Noticeability Scale.

Both interventions were well tolerated. Erythema (grade 3 or 4) was the most frequently observed adverse event, but these episodes were managed effectively and were limited to the small areas being treated. Given the large total number of NB-UVB treatments given across these groups, we feel that this is an acceptable level of erythemas and it is not suggestive of a significant safety risk. The incidence of clinical skin thinning was very low despite the relatively long-term intermittent use of potent topical corticosteroid, including on the face.

All sensitivity analyses were supportive of the main findings and participants who adhered to the treatment regimen (≥ 75%) were more likely to achieve treatment success. There was no difference between the rates of success in the treatment groups that could be attributed to age, skin type or duration of vitiligo.

Relevance to wider literature

The number of participants achieving a treatment success with the trial interventions was low but consistent with findings from other trials. A meta-analysis of studies assessing phototherapy (whole body, as opposed to hand-held) for vitiligo[42], reported that around 19% of patients achieved a 'marked response' (>75% repigmentation) after 6 months of treatment with NB-UVB monotherapy. Participants in our study achieved similar rates of treatment success, as measured using the Vitiligo Noticeability Scale (18% for NB-UVB, 28% for combination at 6 months). The better response rates for vitiligo on the head and neck seen in our study are also consistent with previous findings[42].

There are no other studies that have compared a combination of NB-UVB and mometasone furoate with mometasone furoate alone, so direct comparison with a combination of treatments is not possible. The participants in our study used mometasone furoate on alternate weeks for nine months, which differs from other published studies[37]. We used this alternate week regimen on the basis of feasibility work which suggested that this would be more acceptable than once daily application over a 9-month treatment period.

The Cochrane systematic review of interventions for vitiligo[37] identified a study comparing combination of NB-UVB and clobetasol propionate (a more potent topical corticosteroid) with NB-UVB alone, which suggested that combination treatment might be more effective. However, the study was too small for the results to be conclusive; the relative risk ratio for achieving >75% repigmentation was 1.38 (95% CI 0.71-2.68)[43].

Previous small studies of home-based hand-held phototherapy devices for vitiligo have demonstrated their safety[23,24]; our larger study confirms this. A recently-published study of patients undergoing long-term NB-UVB treatment (mean number of treatments = 211) reported no increase in skin cancer risk, suggesting that treatment can safely be continued for longer periods than in our study, although most patients in the Momen *et. al.* study were skin types IV-VI [44].

Strengths and limitations

This was a large, pragmatic trial that controlled for the commonest causes of bias. The patient-reported primary outcome ensured that treatment success reflected the views of participants and was supported by blinded outcome assessment using digital images.

As found in other vitiligo trials[37], retention throughout the trial was challenging, with just over 70% of participants providing primary outcome data at 9 months, and fewer than 50% providing secondary outcome data by 21 months. Since loss to follow-up was higher than originally anticipated, the trial lacked power to provide a high level of precision around the point estimates.

The most significant drop in the number of participants remaining in the trial was from baseline to first follow-up at 3 months. Many participants commented that the time burden was the main reason for them doing so. Participants who adhered to the treatment regimen ≥ 75% of the time were more likely to achieve treatment success. This requires a significant time commitment, which some participants found challenging. In clinical practice, following such a treatment regimen may not be feasible for some individuals.

Generalisability

This trial has good external validity as it was a large, pragmatic trial with few exclusions, although participants with widespread vitiligo were excluded.

People with all skin types and ethnicities were included in the trial as this reflected the types of patients typically presenting for vitiligo treatment within the UK health service. We did not exclude participants with lighter skin types, as vitiligo can cause considerable distress in such people as well as those with darker skin types[45].

Implications for clinical practice and research

For people with vitiligo requiring second-line therapy, combination treatment with potent TCS and NB-UVB may be helpful. Patients should be informed that only about a quarter of those seeking treatment are likely to achieve a substantial treatment response, that considerable time commitment is required, and response is likely to be slow.

This trial found considerable output variation between individual NB-UVB devices[32], which demonstrates the need for quality assurance testing prior to use. We would recommend any member of the public purchasing such a device seek specialist dermatologist advice and quality assurance before use.

Safety data provide reassurance that mometasone furoate 0.1% used intermittently 'one-week on, one-week off' for up to 9 months is safe for both children and adults. This potent TCS was helpful in stopping the spread of active disease and was successful in 1 in 6 cases, supporting its use as first-line therapy.

Health economic analysis and a process evaluation study were conducted alongside this trial and are reported separately.[32]

Forty percent of participants reported loss of treatment response after stopping treatments. Research into strategies to maintain treatment response are needed.

Conclusion

Combination therapy with both NB-UVB light and potent TCS is likely to result in improved treatment response compared to potent TCS alone, for people with localised

non-segmental vitiligo. Both treatments are relatively safe and well tolerated, but were only successful in around a quarter of participants.

Acknowledgements

The authors would like to thank all those who supported and contributed to delivery of the HI-Light Trial including:

NIHR Clinical Research Network: Assistance in identifying recruitment sites; provision of research infrastructure and staff.

UK Dermatology Clinical Trials Network for help in trial design and identifying recruiting sites. The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network.

We are grateful to Dermfix Ltd (www.dermfix.uk) for providing the NB-UVB devices and dummy devices at a reduced cost. Dermfix Ltd. had no role in design, conduct or analysis of the trial.

Members of the Centre of Evidence Based Dermatology's Patient Panel provided input into the trial design, conduct and dissemination of trial findings. Thanks also to people who responded to online surveys to inform trial design.

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Fleming, Jonathan France, Anthony Dock, Sarah Walton and Paul Creasey); University Hospital Wales, Cardiff and Vale University Health Board (Beverley Gambles, Gladys Makuta and Geraldine Haebich); The Norfolk and Norwich University Hospital, Norfolk and Norwich University Hospitals NHS Foundation Trust (David Tomlinson, Rebecca Phillips, Alison Wiltshire, Aza Yaakub, Urvi Popli, Puran Gurung, Karen Banks Dunnell, Cathy Haughton and Jocelyn Keshet-Price); Solihull Hospital, Heart of England NHS Foundation Trust (Athanasia Filippa, Ruth Jocelyn, Samantha Stafford, Maxine Lovell, Angela Burden, Aaron Wernham, Alexis Cuell, Georgina Fremlin, Helen Goodyear, Indy Atwal, Catherine Cotter, Gabriella Petrof and James Carr); West Glasgow Ambulatory Care Hospital, NHS Greater Glasgow and Clyde (Gabrielle Becher, Anne Thorat, Fiona Cunningham and Cristina MacNeil); Whipps Cross Hospital and The Royal London Hospital, Barts Health NHS Trust (Ceri Guarnieri, Jason Thomson, Satwinderjit Shinhmar, Bibi Badal, Jennifer Ross, Vanessa Van-de-Velde, Claire Marshall Daniel Lieberman, Khatija Sarkar, Adebanke Aboaba, Nadira Qureshi, Maria-Angeliki Gikini, Waffa Girshab, Zeeshaan-ul Hasan, Jonathan Kentley, Sarah Hogan, Darren Hawkins, Denise Andrews, Ausra Zdanaviciene, Chipo Chitsenga, Syed Arafath, Jason Thomson and Beebee Meeajun); Birmingham Children's Hospital, Birmingham Children's Hospital NHS Foundation Trust (Gemma Baker, Jason Pitt, Lucy Cooper, Karen Doherty, Gemma Grovenor, Dharshini Sathish Kumar, Needa Mohamed, Katie Heffernan, Charlotte Cottrill (nee Lilley) and Melanie Rooney); York Hospital, York Teaching Hospital NHS Foundation Trust (Jill Green, Sian Sturdy, Sarah Russell-Sharpe, Helen Marson and David Thompson); Royal Derby Hospital and the London Road Community Hospital, Derby Teaching Hospitals NHS Foundation Trust (Sally-Ann Bell, Vanessa Unsworth, Melody MacGregor, Mariana Bernado, Padma Mohandas, Andrew Martin, Sarah Murfin, William Stone and Michelle Scott); Queens Medical Centre, Nottingham University Hospitals NHS Trust (Jo Llewellyn, Rebecca Phillips and Li-lin Hong); Chelsea and Westminster Hospital, Chelsea and Westminster Hospital NHS Foundation Trust (Miriam Fitzgerald, Charlotte Edwards, Steven Guichard-Kenny, Chris Priest, Amanda Parry, Kribashnie Nundlall, Muna Dahir Hassan, Sarah Riaz, Catherine Sheehan, Rhian Bull, Carina Bautista, Jaime Carungcong, Nicole Kerry, Sathya Visvendra, Mini Thankachen and Elna Cifra); University Hospital of North Durham; County Durham and Darlington NHS Foundation Trust (Anne Thomson, Parastoo Babakinejad and Maneesha Vatve);

The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust (Lisa Fisher, Debbie Banks, Alison Williamson, Louise Palmer, Jessica Hollingsworth, Jackie Dodds, Alycon Walker and Lynsey Searle); Birmingham City Hospital, Sandwell and West Birmingham Hospitals NHS Trust (Christine Baker
Raakhee Ramesh, Anne Rutland, Rohima Khatun, Saibal Sanyal, Sara Mirhadi
Saima Naqvi, Imogen Hughes, Laura Croxton, Sophie Musson, Erin Lynskey, Cat Shuttleworth, Niharika Bansal, Almar Hermosilla, Samia Hussain, Sue Ann Chan and Nadia Shamim).

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Nottingham Clinical Trials Unit: Daniel Simpkins and Chris Rumsey (management of the trial database systems); Jessica Haywood, Sarah Walker, Mathew Foster and Stella Tarr

(data management); Alexandra Erven and Isobel Hawley (blinded control of light devices); Gill Bumphrey and Paula Blance (clinical trials pharmacy); Jenny Smithson and Hayley Gregory (monitoring activities); Melanie Boulter, Sharon Ellender and Hayley Foster (quality assurance).

Centre of Evidence Based Dermatology: Paul Leighton (nested process evaluation), Natasha Rogers (impact and communications, recruitment support, editorial support).

Hillingdon Hospital: Dr Dev Shah, Consultant Dermatologist: Blinded Image Assessment

Data sharing

Anonymised patient level data are available from the corresponding author upon reasonable request.

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Table 1 Baseline characteristics

Characteristic	**TCS**	**NB-UVB**	**Combination**
	(n = 173)	**(n = 169)**	**(n = 175)**
Age at randomisation (years)			
Mean(sd)	38.6[20.0]	36.9[18.9]	37.0[19.1]
Age of adults at randomisation (years)			
Mean(sd)	46.7[15.2]	44.7[14.0]	44.8[14.2]
N	133	130	135
Age of children at randomisation (years)			
Mean(sd)	11.7[3.7]	10.8[3.5]	10.6[3.3]
N	40	39	40
Gender			
Male	75(43%)	88(52%)	105(60%)
Ethnicity			
White	112(65%)	114(67%)	104(59%)
Indian	13(8%)	13(8%)	10(6%)
Pakistani	12(7%)	15(9%)	27(15%)
Bangladeshi	4(2%)	4(2%)	4(2%)
Black	5(3%)	3(2%)	7(4%)
Chinese	2(1%)	1(1%)	1(1%)
Other Asian (Non-Chinese)	5(3%)	6(4%)	6(3%)
Mixed Race	9(5%)	6(4%)	6(3%)
Other	10(6%)	7(4%)	9(5%)
Missing	1(1%)	0	1(1%)
Source of recruitment			
Primary care	35(20%)	36(21%)	47(27%)
Secondary care	74(43%)	67(40%)	72(41%)
Self-referral	64(37%)	66(39%)	56(32%)
Skin phototype			
Type I	2(1%)	2(1%)	5(3%)
Type II	31(18%)	32(19%)	29(17%)
Type III	70(40%)	66(39%)	59(34%)
Type IV	29(17%)	34(20%)	33(19%)
Type V	35(20%)	25(15%)	44(25%)
Type VI	6(3%)	10(6%)	5(3%)
Medical history			
Type I diabetes	5(3%)	3(2%)	4(2%)
Hyperthyroidism	4(2%)	2(1%)	6(3%)
Hypothyroidism	21(12%)	18(11%)	10(6%)
Addison's disease	2(1%)	0	3(2%)

Pernicious anaemia	5(3%)	3(2%)	6(3%)
Alopecia areata	3(2%)	7(4%)	3(2%)
Duration of vitiligo (years)			
Median (25^{th}, 75^{th} centile)	7[3,6]	5[3,11]	7[4,15]
Previous treatments used for vitiligo			
Light therapy	28(16%)	26(15%)	37(21%)
Corticosteroid cream/ointment	80(46%)	75(44%)	80(46%)
Calcineurin inhibitor cream / ointment	51(29%)	39(23%)	56(32%)
Cosmetic camouflage	45(26%)	44(26%)	40(23%)
Other	20(12%)	15(9%)	17(10%)
Target patch location			
Head and neck	53(31%)	52(31%)	56(32%)
Hands and feet	56(32%)	53(31%)	55(31%)
Rest of the body	64(37%)	64(38%)	64(37%)
Number of assessed patches			
1	50(29%)	50(30%)	62(35%)
2	74(43%)	77(46%)	73(42%)
3	49(28%)	42(25%)	40(23%)
Activity of target patch			
Hypomelanotic*			
Definitely	52(30%)	46(27%)	52(30%)
Maybe / No	121 (70%)	123 (73%)	123 (70%)

All data are N unless otherwise indicated.

* It is thought that patches which are hypomelanotic, with poorly defined borders, are more likely to be active, and therefore more responsive to treatment.[38] Patches were assessed at the point of randomisation using Wood's lamp.

	TC (n = 173)	NB-UVB (n = 169)	Combination (n = 175)				
Patient response to VNS scale at 3 months							
More noticeable	16(12%)	26(19%)	15(10%)				
As noticeable	70(52%)	57(42%)	62(43%)				
Slightly less noticeable	34(25%)	34(25%)	47(33%)				
A lot less noticeable	13(10%)	19(14%)	17(12%)				
No longer noticeable	2(1%)	0	2(1%)				
Patient response to VNS scale at 6 months							
More noticeable	11(10%)	23(20%)	10(8%)				
As noticeable	51(44%)	37(33%)	36(29%)				
Slightly less noticeable	37(32%)	33(29%)	45(36%)				
A lot less noticeable	14(12%)	18(16%)	28(22%)				
No longer noticeable	2(2%)	2(2%)	7(6%)				
				Between-group comparisons (ITT)[§]			
Participants with primary outcome at 9 months	**119(69%)**	**123(73%)**	**128(73%)**	**NB-UVB vs TCS**		**Combination vs TCS**	
				Adjusted^ risk difference (95% CI)	Adjusted odds ratio (95% CI)	Adjusted risk difference (95% CI)	Adjusted odds ratio (95% CI)

Patient response to VNS scale at 9 months							
More noticeable	18(15%)	27(22%)	17(13%)				
As noticeable	53(45%)	33(27%)	32(25%)				
Slightly less noticeable	28(24%)	36(29%)	45(35%)	5.20%	1.44(0.77 to	10.94%	1.93(1.02 to
A lot less noticeable	15(13%)	25(20%)	27(21%)	(-4.45% to	2.70)	(0.97% to	3.68)
No longer noticeable	5(4%)	2(2%)	7(5%)	14.85%)		20.92%)	
Patient reported treatment success* using VNS scale at 9 months	**20(17%)**	**27(22%)**	**34(27%)**				

Table 2 Primary outcome analysis

All data are N (%) unless otherwise indicated.

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

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

§ Based on multiple imputation of missing data, pooled treatment success rates from the multiple imputed dataset was 17% for TCS, 23% for NB-UVB and 28% for combination treatment.

Table 3 Secondary outcome: Treatment success by blinded PPI assessors (VNS using digital images at baseline and 9 months)

	TCS	NB-UVB	Combination	Between-group comparisons			
TREATMENT PHASE				**NB-UVB vs TCS**		**Combination vs TCS**	
				Adjusted^ risk difference (95% CI)	Adjusted odds ratio (95% CI)	Adjusted risk difference (95% CI)	Adjusted odds ratio (95% CI)
Treatment success by blinded PPI assessors at 9 months (target patch)	11%(12/112)	20%(22/108)	28%(32/116)	9.70% (1.23% to 18.17%)	2.22(1.14 to 4.31)	16.30% (7.02% to 25.58%)	3.52(1.80 to 6.89)

All data are N (%) unless otherwise indicated.

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

Table 4 Secondary outcome: Percentage repigmentation assessed by blinded dermatologist and investigators

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

All data are N (%) unless otherwise indicated.

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

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

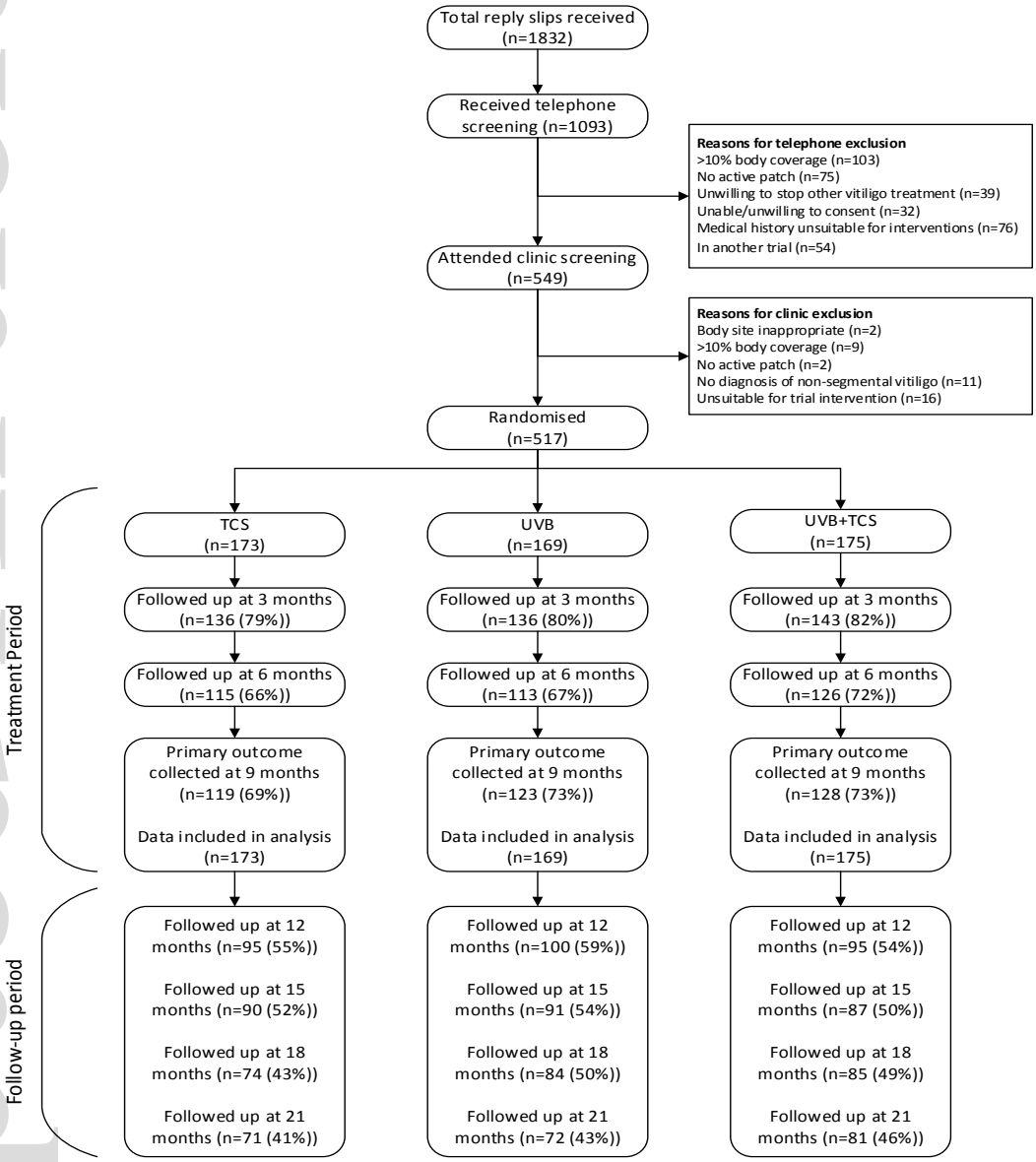
% repigmentation from blinded clinician using digital images was used as main % repigmentation analysis, with missing data replaced by corresponding values from investigator assessments in clinic at 9 months

Table 5 Adverse Events

	TCS	**NB-UVB**	**Combination**
	(n = 173)	**(n = 169)**	**(n = 175)**
Total number of participants reported any related AEs	24(14%)	48(28%)	52(30%)
Total number of reported related AEs	33	69	104
AEs by severity			
Mild	30	32	58
Moderate	3	24	40
Severe	0	13	6
AEs by outcome			
Recovered	20	53	92
Resolved with sequelae	3	6	3
Ongoing	7	5	6
Unknown	3	5	3
Number of erythema events in adults	**2(2)^**	**22(20)^**	**37(26)^**
Grade 3 erythema	0	8	33
Grade 4 erythema	2	14	4
Number of erythema events in children	**1(1)^**	**7(6)^**	**8(7)^**
Grade 3 erythema	1	6	8
Grade 4 erythema	0	1	0
Erythema events by outcome	**3**	**29**	**45**
Recovered	3	25	44
Resolved with sequelae	0	1	0
Ongoing	0	0	1
Unknown	0	3	0
Number of skin thinning* events in adults	**5(5)^**	**2(2)^**	**5(5)^**
Number of skin thinning* events in children	**1(1)^**	**0**	**0**
Skin thinning events by outcome	**6**	**2**	**5**
Recovered	3	1	2
Resolved with sequelae	0	1	2
Ongoing	2	0	1
Unknown	1	0	0

*Skin thinning was defined as any events classified as skin atrophy, skin striae, telangiectasia or spider veins.
^Numbers in parentheses are the total number of participants in whom the adverse event occurred

Figure 1 CONSORT Flow diagram



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