Author's response to reviews

Title: Feasibility, double-blind, randomised, placebo-controlled, multi-centre trial of hand-held NB-UVB phototherapy for the treatment of vitiligo at home (HI-Light trial: Home Intervention of Light therapy)

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Author's response to reviews: see over
Dear Editors

Please receive revised manuscript describing a feasibility, double-blind, randomised, placebo-controlled, multi-centre trial of hand-held NB-UVB phototherapy for the treatment of vitiligo at home (HI-Light trial: Home Intervention of Light therapy). We thank you and the reviewers for these insightful and important comments. We addressed all of them to the best of our ability. The following revisions were made, with 'tracked changes' in the manuscript:

Editorial requests

Request 1: Please remove the funding information and acknowledgments from the title page and place them after the conclusion section.

Revision 1: Done. Page 27-29.

Request 2: Please include a competing interests section at the end of the manuscript, before the reference list. If the authors have no competing interests, please state: "The authors declare that they have no competing interests."

Revision 2: Done. Page 27-29.

Request 3: Please include an Authors' Contributions section at the end of the manuscript, before the reference list. Each author needs to be listed individually. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and
coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Revision 3: Done. Page 27-29

Comment 4: Please also ensure that your revised manuscript conforms to the journal.

Revision 4: References style has been corrected.

Reviewer’s 1 comments (Reviewer: Jinhui Ma)

Comment 1: I think the abstract of this paper need to be revised in order to act as a stand-alone statement that briefly and clearly conveys the essential information of the manuscript. Here I only listed two examples for the authors to consider: (1) ‘examined the feasibility of conducting a large multi-centre RCT on the use of such devices by exploring …’ is the objective of the pilot trial, and it should be move from the Methods section to the Background section; (2) the Results section is not clearly presented. The authors stated that ‘eighty three per cent of people who expressed interest in the trial were willing to be randomised’. It will be helpful to provide readers brief information about who these people are (any vitiligo patients?).

Revision 1: As advised, (1) the objective of the trial has been moved to the background section. Also, clarification regarding the 83% of people who expressed interest was made. The abstract of the trial has been amended as following:

Background

Hand-held NB-UVB units are lightweight devices that may overcome the need to treat vitiligo in hospital-based phototherapy cabinets and allow early treatment at home that may enhance the likelihood of successful repigmentation. The pilot Hi-Light trial (RCT) examined the feasibility of conducting a large multi-centre RCT on the use such devices for the treatment of vitiligo by exploring recruitment, adherence, acceptability and patient education.

Methods

This was a feasibility, double blind, multi-centre, parallel group randomised placebo controlled trial (RCT) of hand-held NB-UVB phototherapy for the treatment of vitiligo at home. The overall duration of
the trial was seven months: recruitment period-three months; treatment period-four months. Participants were randomly allocated to active or placebo group in a 2:1 ratio. The primary outcome measure for this pilot trial was the proportion of eligible participants who were willing to be randomised. The secondary outcomes included: proportion of participants expressing interest in the trial and fulfilling eligibility criteria, withdrawal rates and missing data, proportion of participants adhering to and satisfied with the treatment, incidence of NB-UVB short-term adverse events: erythema (Grade 1-4), pruritus, perilesional hyperpigmentation, hypersensitivity reactions, cold sores, dry skin.

Results

Eighty three per cent of vitiligo patients who expressed interest in the trial (45/54) were willing to be randomised. Due to time and financial constraints, only 29 of 45 potential participants were booked to attend for a baseline hospital visit. All 29 potential participants were confirmed as being eligible and were subsequently randomised into the trial (100%). Willingness to participate in the study for General Practice (family physicians) surgeries and hospitals were 40% and 79% respectively. 86% (25/29) of patients adhered to the treatment. 65% patients (7/11) in the active groups had some degree of repigmentation. Only one patient in the active group reported erythema grade 3 (3%). Both devices were acceptable to participants.

Conclusions

The pilot trial showed that vitiligo patients are keen to participate in trials of home phototherapy. Hand-held narrow band UVB devices need evaluation in the form of a large, pragmatic randomised controlled clinical trial. This pilot trial has explored many of the uncertainties that need to be overcome before embarking on a full scale trial, including the development of a comprehensive training package and treatment protocol. The study has successfully demonstrated willingness of participants to be randomised, very good treatment adherence and repigmentation rates providing evidence of feasibility for a definitive trial.
Comment 2: In the section of ‘Phototherapy for the treatment of vitiligo’ on page 9, the authors mentioned ‘secondary care’. If the authors expect that non-clinical experts would also be the readers of this paper, they should briefly introduce what the primary and secondary care mean.

Revision 2: The following clarifications were made:

- Abstract/Results section: Willingness to participate in the study for General Practice (family physicians) surgeries and hospitals were 40% and 79% respectively
- Main article/Recommendations: Recruitment through primary care (General Practice surgeries).

Comment 3: In the section of ‘Randomisation and blinding’ on page 12, the author stated that ‘permuted blocks of randomly varying size’ was used in the randomization process. The size of permuted blocks could be any integer number between 1 and infinity?

Revision 3: We consulted with the Nottingham Clinical Trials Unit (CTU). We have added the size of permitted blocks as requested: between 3 and 9:

Randomisation and blinding: The randomisation was based on a computer generated pseudo-random code, using random permuted blocks of randomly varying size between 3 and 9, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure and held on a secure University of Nottingham server.

Comment 4: The primary and secondary outcomes described on page 13 should completely match with the primary and secondary objectives of the study. It is not clear which objective was matched with the secondary outcome ‘withdrawal rates and missing data’; and which secondary outcome was matched to the secondary objective ‘to prepare a training package for patients explaining how to use intervention and how to deal with possible side effect.

Revision 4: We have amended the section describing the objectives and the outcomes accordingly:

Objectives

The main aim of this pilot trial was to determine the feasibility of conducting a national, multi-centre, randomised controlled trial (RCT) to determine the effectiveness and safety of home hand-held NB-
UVB phototherapy units both compared to and in combination with topical treatments for repigmentation of early or/and focal vitiligo. The primary objective of this pilot trial was to establish the proportion of eligible patients with vitiligo who are willing to be randomised to home NB-UVB (number of randomised participants/number of eligible participants at baseline). In this trial two different handheld NB-UVB devices, Dermfix 1000 NB-UVB and Waldmann NB-UVB 109, with the same output, but a few differences such as the size of treatment area, weight of the unit, cable length and price. The rational behind using two different devices was to monitor and assess which of the two units was best tolerated in terms of participants’ satisfaction. The information gathered assisted in the choice of device for the main RCT.

An innovative training package was developed for participants explaining how to use the intervention and how to deal with side effects. The successfulness of this training package was established by measuring the following secondary objectives:

- To prepare a training package for participants explaining how to use the intervention and how to deal with possible side effects

- Estimation of withdrawal rates and missing data

- Establishment of participants’ adherence and satisfaction with the treatment

- Establishment of the occurrence of possible short-term side effects i.e. if the device is suitable for home use with limited medical supervision

Another secondary objective of this pilot trial was:

- To test feasibility outcomes for the main RCT including repigmentation, cessation of spreading of the disease, impact on quality of life, global improvement in vitiligo, patient’s benefit index.

Outcomes

The primary outcome measure for this pilot trial was the proportion of eligible participants who were willing to be randomised (number of randomised participants/number of eligible participants at baseline).
The secondary outcomes were:

- Proportion of participants expressing interest in the trial (number of participants pre-screened/number of invitation sent) and fulfilling eligibility criteria (number of participants eligible at baseline visit/number of participants pre-screened)

- Withdrawal rates and missing data

- Proportion of participants adhering to and satisfied with the treatment (number of participants who complied with the treatment regimen/total number of randomised participants). Adherence was monitored using all of the following parameters:
  - Three to four treatment sessions per week
  - At least one day should be left between consecutive treatment sessions
  - If a treatment session was missed due to side effects and the treatment plan was resumed correctly, participants were considered compliant with the treatment plan.

- Incidence of NB-UVB short-term adverse events: erythema (Grade 1-4), pruritus, perilesional hyperpigmentation, hypersensitivity reactions, cold sores, dry skin.

- Proportion of participants and assessors for whom the blinding of the allocated group (active/placebo) was maintained

- Outcome measures for the main large trial were also tested:
  - Repigmentation: Repigmentation rate of vitiliginous lesions presented in percentage of repigmentation quartiles: negative-0%, 1-24%, 25-49%, 50-74%, 75-100%. Convatec transparencies were used to trace the lesions at baseline and week 16 visits. These were measured by using the ImageJ 1.47d (Image processing and analysis in Java by the National Institute of Health, USA; [http://imagej.nih.gov/ij](http://imagej.nih.gov/ij)).
o Cessation of spreading of vitiligo during the past year i.e. no new vitiliginous lesions or no increase in size of existing vitiliginous lesions in the last 12 months.

o Impact on the quality of life of participants: Dermatology Life Quality Index (DLQI) [13] and Children Dermatology Life Quality Index (CDLQI) [14] on baseline and week 16 visits.

o Global improvement in vitiligo: 5-point Likert scale (much worse; a bit worse; no change; a bit better and much better)-at week 16 visit.

o Patient Benefit Index [15] (PBI)-at baseline and week 16 visit.

o Colour match of newly repigmented vitiliginous lesions (bad, fair or excellent). Patient and research nurse were asked to rate the colour match of each representative lesion at week 16 visit. This outcome was subjective.

Comment 5: In the section of ‘Outcomes’ on page 13, a few outcomes were not clearly defined. For examples (1) how the secondary outcomes ‘proportion of participants expressing interest in the trial and fulfilling eligibility criteria’ were calculated (i.e. what are the denominators and numerators); (2) what is the definition of ‘cessation of spreading of vitiligo during the past year’; (3) what are the definitions for bad, fair or excellent colour match of newly repigmented vitiliginous lesions; (4) what is the definition of ‘adhering to the treatment’ (for example, complete more than 80% of scheduled treatment sessions per week and treatment times?) etc.

Revision 5: The following changes were made in the outcomes section (page 15):

(1) Proportion of participants expressing interest in the trial (number of participants pre-screened/number of invitation sent) and fulfilling eligibility criteria (number of participants eligible at baseline visit/number of participants pre-screened.

(2) Cessation of spreading of vitiligo during the past year i.e. no new vitiliginous lesions or no increase in size of existing vitiliginous lesions in the last 12 months.
(3) Colour match of newly repigmented vitiliginous lesions (bad, fair or excellent). Patient and research nurse were asked to rate the colour match of each representative lesion at week 16 visit. This outcome was subjective.

(4) Proportion of participants adhering to and satisfied with the treatment. Adherence was monitored using the following parameters:

- Three to four treatment sessions per week
- At least one day should be left between consecutive treatment sessions
- If a treatment session was missed due to side effects and the treatment plan was resumed correctly, participants were considered compliant with the treatment plan.

Comment 6: The author did not mention if the patients got any other treatment such as topical steroids besides the NB-UVB device.

Revision 6: No concurrent treatments during the trial were allowed as stated in the “Participants and settings” section (page 14): No therapy for vitiligo in the previous two weeks and no other concurrent vitiligo treatments during the trial were allowed).

Comment 7: In the section of ‘Withdrawals’ on page 17, I think it is helpful to provide the readers the intervention group for each of the 3 participants who withdrew from the study.

Revision 7: We believe this information was already provided. Please see “Withdrawals”, page 19: “Three of 29 participants (10%) withdrew from the treatment (two patients from the active group and one from placebo group)”.

Comment 8: In the section of ‘Side effects’ on page 18, I would like to see the frequency of side effects across different treatment groups.

Revision 8: In addition to the already provided information on frequency of side effects in both groups, we added the following (in bold):

Twenty seven (8/29) and thirteen per cent (4/29) of participants in the active group reported erythema grade 1 and 2 respectively. Only one patient reported erythema grade 3 (3%). Other side effects included: pruritus (2/29; 7%), hyperpigmentation around the lesions (3/29; 10%) and dry skin (3/29;
10%), cold sores (1/29; 3%). In the placebo group, two patients reported erythema grade 1 (2/29; 6%). **No other side effects were reported in the placebo group.**

*Comment 9*: Table 3 second line: what is the meaning of “-0”?

*Revision 9*: This is now changed to “negative”-0.

*Comment 10*: There are two Table 4s. One should be changed to Table 5.

*Revision 10*: Table 5. Repigmentation in the placebo group for each anatomical site per participant

**Reviewer’s 2 comments** (Reviewer: Rong Chu)

*Comment 1*: Introduction. Scientific background for the main study has been provided. Can the authors also explain the rationale for assessing feasibility in this pilot study? What was the rationale for choosing and comparing the two different NB-UVB devices in the pilot?

*Revision 1*: The following paragraph was added in the objectives section (page 11):

In this trial two different hand-held NB-UVB devices were explored, Dermfix 1000 NB-UVB and Waldmann NB-UVB 109, with the same output, but a few differences such as the size of treatment area, weight of the unit, cable length and price. The rationale behind using two different devices was to monitor and assess which of the two units was best tolerated in terms of participants’ satisfaction. The information gathered assisted in the choice of device for the main RCT.

*Comment 2*: Objectives. (1) Please state the objectives and hypothesis for the main trial, followed by the objectives of the pilot study. (2) “The primary objective of this pilot trial was to establish the proportion of eligible participants …” A proportion is meaningful when the numerator and denominator are specified. What are numerator and denominator populations here? (3) “To establish … side effects” as a secondary objective is confusing. Did the authors mean to establish or assess the incidence/occurrence of side effects, or to define what the side effects are and how they can be measured? Please clarify the third secondary objective also.
Revision 2: The following changes were made:

(1) The main aim of this pilot trial was to determine the feasibility of conducting a national, multi-centre, randomised controlled trial (RCT) to determine the effectiveness and safety of home hand-held NB-UVB phototherapy units both compared to and in combination with topical treatments for early or/and focal vitiligo.

(2) The primary objective of this pilot trial was to establish the proportion of eligible patients with vitiligo who are willing to be randomised to home NB-UVB (number of randomised participants/number of eligible participants at baseline).

(3) Establishment of the occurrence of possible short-term side effects i.e. if the device is suitable for home use with limited medical supervision.

Comment 3: Outcomes. Please specify the primary and secondary outcomes of the main trial and align them with the objectives of the main trial. If the suitability of the primary outcome cannot be determined prior to the completion of the pilot trial, include this as part of the feasibility outcomes. Would repigmentation be analyzed as a count, binary value (presence yes or no) or other types of variable? For the proportion outcomes in the pilot trial, please ensure the numerators and denominators can be perceived without ambiguity.

- Revision 3: These points have been partially addressed in the response to reviewer 1, revisions 4-5 as outlined above. It is the case that one of the main functions of the pilot trial was to test the use of different outcome measures for use in the subsequent trial; as a result it is not possible to specify what the primary outcome for the main trial will be at this stage. We have clarified this in the text:
  - To test feasibility outcomes for the main RCT including repigmentation, cessation of spreading of the disease, impact on quality of life, patient's benefit index and colour match.

Also, the following paragraph has been added to the discussion section/recommendations for future trials:
Recommendation 3: Outcomes for the main trial. On the basis of the results of the pilot trial, the following outcomes are recommended to be included in the main trial: repigmentation, patient reported success, cessation of spreading of vitiligo and impact on quality of life of vitiligo patients, amongst others that researchers deem appropriate for their trial. Also, based on the above recommendation (see recommendation 2), researchers should consider choosing patient reported success rather than repigmentation as primary outcome. Although the former is a subjective outcome, perhaps it captures better several aspects of repigmentation such as pattern of repigmentation, colour match of newly repigmented lesions and percentage of repigmentation (size of vitiligious lesions).

- Analysis of repigmentation of vitiligious lesions has been clarified:
  - Repigmentation rate of vitiligious lesions presented in percentage of repigmentation quartiles: negative-0%, 1-24%, 25-49%, 50-74%, 75-100%. Convatec transparencies were used to trace the lesions at baseline and week 16 visits. These were measured by using the ImageJ 1.47d (Image processing and analysis in Java by the National Institute of Health, USA; http://imagej.nih.gov/ij).

Comment 4: Results, recruitment. Please add fractional numerator and denominator next to the rates, e.g. response rate = 79%.

Revision 4: The following numerators and denominators were added (in bold): We received 38 (response rate=79% (38/48)) completed reply slips from patients, who were willing to be contacted (Nottingham response rate=93.5% (29/31); Leicester response rate=53% (9/17)). In addition, two GP surgeries (one in Leicester and one in Nottingham) sent 67 invitation letters. From these, we received 28 completed reply slips (total response rate=40% (28/67)). Fourteen patients were interested in the trial (response rate=19% (14/74)).

Comment 5: Results. What was the finding on missing data assessment which was mentioned as a secondary outcome in the Methods section?

Revision 5: The following paragraph was has been added to the results section: All participants, except one who was lost to follow-up, completed the end of study questionnaire in full (28/29; 96.5%). The DLQI and PBI questionnaires at baseline and week 16 were completed by 96.5% (28/29) of
participants also; at baseline one participant did not complete the questionnaires. One missing diary and week 16 questionnaire (3%; 1/29) belonged to the lost to follow-up patient. The research team made every effort possible to contact and find the patient, including reaching out to his regular GP. Unfortunately neither the diary nor the device were recovered.

I am looking forward to hearing from you and please do not hesitate to contact me if any enquiries.

Thank you very much for your consideration.

Kindest regards

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(on behalf of the writing team)

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