Author's response to reviews

Title: Temperature-controlled Laminar Airflow in Severe asthma for Exacerbation Reduction (The LASER Trial): Study protocol for a randomised controlled trial.

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Author's response to reviews: see over
Responses to Reviewers for manuscript currently entitled:

“A multi-centre randomised, double blind, placebo-controlled, parallel group trial of the effectiveness of the nocturnal use of a Temperature Controlled Laminar Airflow (TLA) Device (Airsonett®) in adults with poorly-controlled, severe allergic asthma (LASER trial): Study protocol for a randomised controlled trial”

Dr Will Storrar et al.

Reviewer: Yong-Qing Yang

Major Revisions:

Q1. The objective of this trial is to assess the efficacy of the new treatment, however, there is no waiting list control and positive drug control.

A1. Waiting List Control:
The reviewer highlights some important points. We have reduced the risk from waiting list bias by having a protocol requirement for the device to be installed within 10 days of randomisation, and any excursions beyond that will be treated as a protocol deviation. This will ensure every device is installed by the study engineering team swiftly to minimise any delay in initiating treatment for either index or placebo groups. The study engineering teams will also be blinded to the allocation, and as the placebo TLA device is indistinguishable from the treatment device, there will also be no bias from order of preference in device installation.

Positive Drug Control:
In this pragmatic Trial, all participants will continue to receive their daily inhaled and oral medication for treatment of severe allergic asthma, and we have specified the minimum number of asthma controller medications required for Trial entry. The placebo group will therefore continue to receive usual medications, and therefore not be true placebo by receiving no treatment at all. Addition of another asthma controller drug in the placebo group over and above the usual medications, would in our view make the groups incomparable, and add significant cost to the Trial because of expensive, additional controller therapies.

Q2. Why the study was conducted at night? Will the author compare the effect of the treatment at daytimes?

A2. The vast majority of the total personal exposure to the main indoor allergens occurs at night during sleep, largely through house dust mite exposure from bedding, pillows and mattresses; the contribution of daytime exposures to the overall personal exposure is therefore similarly low in the majority of participants. The intervention device thus targets the period of exposure when individuals with allergic asthma receive their greatest exposure and when they are at highest risk. The reasons for treatment at least at night is a very practical one: we cannot conduct a trial where we can expect participants to spend the vast majority of their time in bed to enjoy the
potential benefit of the device in the day time, nor is the device portable enough where we can expect participants to wheel it around as part of everyday activities. We will however ask participants to record times when they may use the device at additional times either in the day or longer at night in a daily “Device Usage” diary. We will have a record of the total daily hours when the device was on, and presumably being used by the participant, and thus use this in our analyses of effect.

Q3. When the author calculated the sample size, how to set the standard deviation? Please provide the formula.

A3. The sample size calculation is based on a Poisson regression model\(^1\), therefore it only requires a single parameter, i.e. the expected exacerbation rate, for the calculation, since the mean and variance of a Poisson-distributed random variable are both equal.

\(^1\) Signorini, David. 1991. ‘Sample size for Poisson regression’, Biometrika, Volume 78, 2, pages 446-450.

Q4. What are the limitations of the study?

A4. The following limitations have been identified:

Recruitment and Retention: As with many randomised controlled trials, there are challenges with recruiting to time and target as specified in the Trial protocol and within funding budgets. Given that the Trial is investigating a new treatment device which is installed in participant’s homes, there is a burden on participants that might lead to participants withdrawing from the Trial. It will be important to understand barriers to recruitment and retention of participants and we will be conducting qualitative interviews with Trial participants to gain a better understanding of factors which might influence participants adherence to treatment and retention in the Trial.

Adherence to treatment: Although we are asking participants to report use of the device and plan to corroborate this with the number of hours that the device reports that it has been used, there is a risk that participants may not use the device and may not report this to the trial team.

Difficult Patient Population: The population being studied is a difficult population often with multiple physical and psychological comorbidities. The patient group that we are looking for has unstable disease as we require participants to have had at least 2 courses of steroids in the preceding 12 months. Many have required steroids much more frequently than this and finding a period of stability when they can be enrolled may prove challenging.

Data Completeness: As with any trial with large numbers of data points, there is a risk of receiving poor quality or incomplete data.

Q5. From the registration information of ISRCTN46346208, the overall start date of the study is Dec 1st, 2013 and the registration date is Jan 15th, 2014. Why the
registration date is later than the overall start date?

A5. The start date of Dec 1st 2013 refers to the start of funding from the NIHR, while the 15th Jan 2014 refers to the date of accepted registration with the ISRCTN.

Minor Revisions:

Q1. The title should be modified in order to avoid redundancy.

A1. The title has been shortened as follows to avoid redundancy:

Temperature-controlled Laminar Airflow in Severe asthma for Exacerbation Reduction (The LASER Trial): Study protocol for a randomised controlled trial.

Q2. The citation format should be changed.

A2. It is the authors understanding that the citation format that has been used is that required by the Trials journal. If this is not the case then this can be updated accordingly.
Reviewer: José Antonio González Alastrué

Minor Revisions:

Q1. I would ask the authors to clarify a bit the definition of the primary outcome measurement. They say that the patient will keep an "exacerbation diary", and they will be asked to contact the medical team "within 72 hours": It's not clear to me if the count of episodes will be mainly (or only) based on the patient notes or on contrasted reports received by the local trial team.

A1. Daily symptoms are common in severe asthma, so the Trial required a clear definition of an exacerbation that distinguished it from other minor increases in daily symptoms. We propose to use the internationally accepted American Thoracic Society/European Respiratory Society joint guideline definition of an asthma exacerbation which is: ‘A worsening of asthma requiring systemic corticosteroids, ≥30mg prednisolone or equivalent daily (or ≥50% increase in dose if maintenance 30mg prednisolone or above) for 3 or more days.’

The purpose of an Exacerbation Diary in this Trial is two-fold: firstly, to help the participant record symptoms, peak flows and use of reliever medication as well as commencement of oral corticosteroids, as this clinical information will be important to the Trial team to corroborate the exacerbation (as the participant will be asked to visit the Trial team after 72 hours of commencing the oral corticosteroids). The second reason for the diary is to remind the participant to contact the Trial team, but only once they have completed 72 hours of the oral corticosteroid treatment as part of their usual emergency care and not before; a visit earlier could lead to bias if the Trial team is then involved in clinical decisions that may potentially affect whether the patient completes at least 72 hours of treatment or not, and thus affect the primary outcome variable. We will therefore only use those exacerbations verified by the Trial team in the final analyses. Participants are also asked about exacerbations at all follow up visits to ensure that no events have gone unreported.

Q2. "Methods" described in the Abstract say: 'A total of 222 patients [...] will be minimised ...' I would find the expression more accurate if it just says "allocated" or "assigned". I think that the authors mean that a minimisation algorithm is employed to allocate the patients to an intervention; this issue could be skipped in the Abstract section, in my opinion.

A2. Acknowledged - changed in the document to “assigned”

Q3. I would recommend that the authors add the approval date (26 February 2014) by the NRES Committee instead of the reference. This is important to emphasize that the ethical approval was prior to beginning patient enrolment.

A3. Acknowledged – date of ethical approval added to document.

Q4. Although they are likely well known, some abbreviations are missing from the List (e.g. GCP). The "Sino-Nasal Outcome Test" looks a bit strange: probably the term "22-item" should appear at the right instead of the left side.
A4. Acknowledged and updated.

Q5. I haven't found any mention of plans for communicating important protocol amendments (SPIRIT, item 25).

A5. An additional paragraph has been added stating:

**Protocol Amendments**
Protocol amendments will be agreed with the Trial Steering Committee, Data Safety and Monitoring Committee, Sponsor and Funding Body prior to submission for ethical approval. Following ethical approval, protocol modifications will be communicated with relevant parties such as the trial investigators, the trial registry and, if required, trial participants.
Changes made to the original manuscript:

1. In response to the reviewer’s comment above related to title redundancy, the title has been shortened to: Temperature-controlled Laminar Airflow in Severe asthma for Exacerbation Reduction (The LASER Trial): Study protocol for a randomised controlled trial. (Page 1)

2. The Date and Version Number of the protocol has been updated reflecting a recent protocol amendment since the original manuscript was submitted (Page 1)

3. Minimised has been changed to assigned in line with the 2nd reviewer’s comment (JAGA). (Page 2)

4. The inclusion criteria section has been updated to reflect the recent protocol amendment to include participants of 16-75yrs (previously 18-75yrs), ICS dose has been changed to ≥1000 (previously >1000) and exacerbation free for at least 2 weeks (previously 4 weeks). (Pages 6 and 7)

5. Minimised changed to assigned as above (Page 8)

6. Date of ethical approval added (Page 17)

7. A paragraph related to Protocol Amendments has been added in line with the 2nd reviewer’s comment (JAGA). (Page 18)

8. The number of actively recruiting trial centres has been updated to 14 (previously 10) (Page 19)

9. List of abbreviation updated to include GCP and to re-order SNOT-22 (as per 2nd reviewer’s comment (JAGA) (Page 20)

10. Non-contributing authors removed from the contributing authors section as requested by the editorial team (Page 21)