Author's response to reviews

Title: The Preloading Trial: An open label pragmatic randomised controlled trial of nicotine preloading for smoking cessation

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Author's response to reviews: see over
19th March 2014

Dear Sir

Re: MS: 8989030571127274
The preloading trial: study protocol for an open label pragmatic randomised controlled trial of nicotine preloading for smoking cessation

I am writing to you following your email of the 28th February 2014, which included instructions on how to revise our manuscript (detailed above), for publication in your journal.

Please find enclosed our revised manuscript with track changes and a response to your comments below. The main manuscript document and Additional Files 1&2 have revisions and Figure 2 has been removed; whereas Figure 1 is as previously submitted.

I hope this is all to your satisfaction; however if there are any problems then please let me know.

Yours Faithfully

Nicola Lindson-Hawley
(Trial Manager)
Response to Editor and Reviewer comments

Editorial requests
Please modify your Authors Contributions section to demonstrate that each author meets all three of the following criteria to qualify for authorship:

- Substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published

Currently GD does not meet point 1.

Authors Contributions amended as follows:

‘NL-H, GD and PA drafted the manuscript and contributed to the design of this study. MM designed and drafted the genetics element of the study, contributed to the wider study design, and made comments on the manuscript. Authors AM, HM, PH, SL and TC contributed to the design of this study, and made comments on the manuscript. SP designed and drafted the health economics evaluation element of the study; DL aided in the design and drafted the weight change element of the study. All authors read and approved the final manuscript. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR HTA programme, NIHR, NHS or the Department of Health.”

Graeme Docherty created the first draft of the manuscript and as such contributed to early design decisions.

Major comments
The authors’ comments raise two major new questions: is the aim to study efficacy or effectiveness; and what type of trial is it. These two questions are linked but will be commented separately.

Efficacy or effectiveness
On the one hand there is an argument for an efficacy trial as stated in the Abstract:
“This large trial will add substantially to evidence on the efficacy of nicotine preloading, but also on its cost effectiveness and potential mediators, which have not been investigated in detail previously.”
and in the Trial objectives:
“To examine the relative efficacy of nicotine patch worn for 4 weeks prior to quitting plus standard NHS care post-quit versus standard care only in smokers undergoing NHS treatment for tobacco dependence.”
On the other hand there seems to be some ambiguity in the first paragraph of the Discussion, where instead effectiveness is presented as the outcome:
“the use of a pragmatic design, which mimics how the preloading intervention would be carried out in practice, means that resulting relative estimates of effectiveness will more accurately represent what we would expect to see if the intervention were carried out in a real-world setting.”
although efficacy is again mentioned later in the same paragraph:
“power to detect useful differences in efficacy between usual smoking cessation
support and the addition of nicotine preloading treatment to this support". To add to the confusion, it is stated in the final paragraph of the Discussion that the primary research question is: “the effectiveness of preloading”. I think it is necessary for the authors to clarify how they view this issue. For me it is difficult to combine the following response to one of my review comments with a trial aiming to determine efficacy: “This trial has been designed to replicate clinical practice. In clinical practice clinicians make judgements about suitability for treatment and they do not use cut-offs. We therefore give our clinicians a broad framework and encourage them to assess suitability as they would outside of a trial …”

We agree- the most appropriate term in this case is effectiveness, as we are carrying out a pragmatic trial. All mentions of efficacy in the manuscript relating to the trial (including those specified above) have been changed to effect/effectiveness.

Type of trial
I used the term ‘behavioural intervention’ in my previous review, and the authors’ response is that that was incorrect, they call it a pharmaceutical trial: “this trial is a trial of a pharmaceutical and is not a test of a behavioural intervention. Moreover, it is regulated as a pharmaceutical trial. …the standards that apply to testing a brand new pharmaceutical that does not have a marketing authorisation apply to this trial under EU law.”

I can agree that it was not appropriate to call it a behavioural intervention trial, although the primary outcome is behavioural. However, the authors also use the term “smoking cessation trial”, which sounds more towards the behavioural field. More pertinent is that the authors talk about a “brand new pharmaceutical” in their response. This is quite surprising to me as this information is not present in the manuscript. Instead the authors have commented in their literature review that “There are two previously published systematic reviews of nicotine preloading [6, 7]. These reviews both reported very positive results for preloading”.

By reading the manuscript, I have not understood that the aim of the trial was to test a “brand new pharmaceutical”, not even a new indication for an established drug with known spectrum of adverse drug reactions and side-effects.

We think that the use of the term smoking cessation trial is acceptable in the context that it is used as we are referring to the use of intention to treat analyses across smoking cessation trials (be they pharmaceutical or behavioural) rather than in the case of the specific trial.

Secondly we think the reviewer may have misunderstood the meaning of the below in our first response:

“We agree with the reviewer that there is no real risk but the standards that apply to testing a brand new pharmaceutical that does not have a marketing authorisation apply to this trial under EU law.”

What we meant by this was that although this trial is a trial of an authorised medicinal product that has been on the market for a long time we still have to be regulated by the MHRA, as the medication regimes differ across trial arms (technically making this trial a clinical trial of an investigational medicinal product (CTIMP), in the same way that a trial of ‘a brand new pharmaceutical’ would need to. Therefore the reviewer was right in thinking that this is not a trial of a new drug or indication.

Length of article
It is commendable that the authors have reduced the length of the manuscript by
moving some parts to appendices. However, the authors argue that there is a limit to this as “The protocol follows that approved by the sponsor and in many respects it is a legal document, approved by the UK medical regulator. It specifies its format and this necessitates the stylised form which necessitates some repetition.”

This shows, in my judgement, a misunderstanding of the type of manuscript the journal expects. It is not to present a formal study protocol, but a description of such a protocol in sufficient detail so that it can be replicated and including a discussion about strengths and limitations. The article in Trials will not be a legal document and there should be no reason for sponsors or regulators to approve the text, although the authors may want their comments. The authors should have the sole responsibility for the manuscript and decide about the content.

We have been through the manuscript again and have tried to remove any unnecessary text and any repetitions. In particular duplicates have been removed from the ‘Assessment’, ‘Data handling...’, ‘Regulatory Issues’ and ‘Publication’ sections.

We have also removed all text relating to the weight and genetic analyses in the main manuscript, as it is not usual to report all potential secondary observational analyses that may be carried out on trial data. We have moved it into Additional File 1.

**Minor comments**

Good that the status of recruitment has been added. It shows that 55% of the target number has been reached after about 18 months. It would be interesting to get some further information about how this recruitment has taken place, as the authors have described one main recruitment strategy and some alternative ways if recruitment slows down. Have these alternative routes been used?

A sentence has been included in this section specifying that recruitment rates were not as high as expected early in the trial and therefore the whole range of recruitment strategies listed earlier in the manuscript are being used:

“As response rates to letters from GP practices and the London smoker’s clinics advertisements have been lower than expected, these core recruitment strategies have been supplemented by the additional strategies listed in the ‘Recruitment’ section above.”

**Edits**

There are a few spelling mistakes, for example:

Page 46, line 6: should be ‘associations’

This has been corrected and another full spell check of the document was carried out. Any minor mistakes have been rectified.

**References**

Mostly correct.

A few remaining mistakes:

1. No capital letters in ordinary words in titles: ref # 29, 31, 32, 35
2. Volume and page numbers missing: ref #31
3. Title should be in bold: ref #61
4. Correct line spacing: ref #61
5. No space before page numbers: ref #47
6. Location of publisher should come before name: ref #41, 60 (cf. ref #56)

All corrected. Some references have now been moved to Additional Files as appropriate.
In addition:

- Due to the order they are now cited in the text/tables, the numbering of Additional Files 1 and 2 have been swapped.
- Figure 2 has been removed as it was only cited in Additional File 2 (no longer the main manuscript) and this level of detail in AE reporting is not warranted.