Reviewer’s report

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

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Reviewer: Rolf Wahlstrom

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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 …”

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.

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.

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?

Edits
There are a few spelling mistakes, for example:
Page 46, line 6: should be ‘associations’

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)