Reviewer’s report

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

Version: 2 Date: 2 January 2014

Reviewer: Rolf Wahlstrom

Reviewer’s report:

General
This manuscript describes a pragmatic intervention study on a topic where existing evidence is scarce. Most of the aspects related to the background and justification of the study, as well as recruitment of participants, allocation to study arms, intervention components, data collection, outcome measures and analysis are well described, although in parts too detailed. The manuscript is very long and one whole section can be deleted. Furthermore, there are a few issues that need more detailed description in the text and related comments in the Discussion, as pointed out below.

Necessary revisions

1. Sample size (p. 43)
a) The sample size calculation is only based on the primary outcome, which could be commented in the Discussion, including how strong the statistical analysis can be presumed to be for secondary outcomes; b) Nothing is mentioned about attrition, but this can be assumed to become an issue if I understand the study design correctly. If not, the authors should explain why.

2. Initial assessment (p. 16)
Pre-enrolment, potential participants will be judged regarding “suitability for preloading”. Four criteria on which this judgement should be based are described, but not how the cut-off levels are defined, for example, how long time for the first cigarette in the morning or how many cigarettes per day, or what level of exhaled CO. This should be clarified, otherwise it is not possible to replicate the trial.

3. Treatment withdrawal (p. 17)
It is stated that participants who have previously had severe adverse reactions (of NRT) will be excluded from the trial. My question is why this has not been one of the exclusion criteria? It is obviously something that is known already at recruitment.

4. Partner allocation (p. 18)
The authors argue that couples should have separate allocations, but these arguments are not quite convincing. I agree that both should not automatically be
allocated to the same arm, but is the risk of introducing a clustering effect really that big and bigger than other risks of interaction between the partners? Why couldn’t both be randomly allocated in the same way as other participants? Such a procedure would yield four possible outcomes (both to intervention, both to control, partner 1 to intervention, or partner 2 to intervention). I think that would have been a stricter way of allocating participants. Further, it is not mentioned how the allocation within the couple will be arranged.

5. Pharmacovigilance
This whole section should be removed from the manuscript and put in an additional file. The trial is behavioural, using a well-known pharmaceutical product, not testing a new one.

6. Length of article
The manuscript is too long, even after the section on Pharmacovigilance has been removed. There are some repetitions, which should be adjusted. The information about weight measurements (p. 45-46) is too detailed and can be drastically reduced or moved to an additional file.

Minor revisions
1. Page 9, 3rd paragraph, line 3-5: The two sentences “There is good evidence that adherence to NRT … enhances cessation” and “Four studies … none of these showed enhanced adherence post-cessation”, seem to be contradictory. Some clarifications is needed.

2. The abbreviation CRF is mentioned for the first time on page 34 (if I haven’t missed any previous use), but is not explained until on page 48 and then in a heading (a common rule is not to explain abbreviations in headings).

3. Page 24, first sentence. I think this sentence should be rewritten for clarity. It is, at least for me as non-native English speaker, possible to misunderstand the text to mean that there will be no intervention with standard stop-smoking treatment. It would be much clearer to write: “… the comparator to preloading will be standard stop-smoking treatment, but no (other) intervention.

4. Page 25, Trial behavioural support, 6th line: The expression “-3 visit” should be changed to ‘second visit’ or ‘one-week visit after baseline’ or similar expression as this has been used in the description of the intervention (p. 24) and in Fig. 1.

5. Page 38-39, last and first line, respectively: It would be informative if authors could add how the items on “rate your chances of giving up smoking for good” and “How important is it for you” will actually be measured. Will there be predefined answers as for other questions, or open rating?

6. Trial status (p. 55)
Add the number of participants that have been recruited until now.

Edits
Page 55, 3rd line from bottom: change to 'a clinical trial'
Page 55, bottom line: change to: ‘prevention’
Page 56, 2nd line: delete ‘&’
Page 56, 8th line: delete one full stop

References
The instructions have been followed to a large extent, except that journal names have not consistently been abbreviated. This must be revised.

Additionally there are some other mistakes:
1. Volume should be in bold: ref # 57
2. No capital letters in ordinary words in titles: ref # 5,10,11,16, 28, 29, 37, 45, 47
3. Location of publishing authority not mentioned: ref #21, 41, 60
4. Not necessary to add doi for journal articles: ref #25, 36, 47, 54, 57
5. Page numbers missing: ref #25