PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomized, placebo controlled, double blind, double dummy, multicenter trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine; the ECSMOKE trial protocol.
AUTHORS	Berlin, Ivan; Dautzenberg, Bertrand; Lehmann, Blandine; Palmyre, Jessica; Liegey, Emmanuelle; De Rycke, Yann; Tubach, Florence

VERSION 1 - REVIEW

REVIEWER	Jamie Hartmann-Boyce University of Oxford, UK
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	This is an important study and I very much look forward to seeing its results, and hope its conduct goes smoothly. I have a few suggestions: 1. The paper would benefit from a thorough copyedit as there are quite a few grammatical errors and typos - however, I definitely don't think this is a reason not to accept the paper 2. I think follow-up at six months is critical to helping contribute to knowledge in this area, but I'm not clear on whether smoking cessation will be measured to this point (page 13, line 19 suggests it will only be measured at visits 1 through 5 but can the authors confirm as if so what is the point of visit 6 (line 57) and why not measure abstinence then, plus info on page 15 suggests abstinence will be measured at all follow-up points) 3. How will the blood pressure data be analysed and used? 4. You may want to consider involving PPI representatives to help shape dissemination plans as this is likely to generate considerable public interest 5. Page 10, line 55 - note combined NRT (short + long acting form) appears as effective as varenicline, so this statement is only true for single form NRT 6. Page 19, line 43 - don't understand why there is a question mark - is this incomplete?

REVIEWER	Joanna Chu National Institute for Health Innovation, University of Auckland, New Zealand
REVIEW RETURNED	03-Feb-2019

GENERAL COMMENTS	The study is well designed with objectives, methodology and procedures well described. Good clinical practice guidelines are followed and risk and safety assessments have been considered. Please consider the following for the Introduction section. The authors only describe a small amount of studies on EC as an aid to quit smoking. A discussion on harm reduction approach would strengthen the introduction and provides a stronger rationale for the study. Furthermore, discussion on safety of EC should be addressed. Currently, the authors omits the controversies around ECs and should be in part acknowledged. For example, the authors state in the article "observational cohorts provided conflicting results as an aid to quit smoking and will not be mentioned further".

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1

The paper would benefit from a thorough copyedit as there are quite a few grammatical errors and typos - however, I definitely don't think this is a reason not to accept the paper.

Response: Thank you for your comment. We have revised again the text for errors.

2. I think follow-up at six months is critical to helping contribute to knowledge in this area, but I'm not clear on whether smoking cessation will be measured to this point (page 13, line 19 suggests it will only be measured at visits 1 through 5 but can the authors confirm as if so what is the point of visit 6 (line 57) and why not measure abstinence then, plus info on page 15 suggests abstinence will be measured at all follow-up points).

Response: Thank you for this remark. Evidently smoking abstinence will also be measured at Visit 6. We corrected this omission.

3. How will the blood pressure data be analysed and used?

Response: Blood pressure data will be analysed as other variables as indicated on page 19, last paragraph: “Variables collected at different visits will be analysed in longitudinal, linear or logistic random effect models.”

4. You may want to consider involving PPI representatives to help shape dissemination plans as this is likely to generate considerable public interest.

Response: We added to the Ethics and Dissemination chapter that our institution’s Press Department will help prepare a dissemination plan about patient and public involvement (PPI) in the research.

5. Page 10, line 55 - note combined NRT (short + long acting form) appears as effective as varenicline, so this statement is only true for single form NRT

Response: We agree. We modified this sentence and added the 2 corresponding Cochrane reviews’ references.

6. Page 19, line 43 - don't understand why there is a question mark - is this incomplete?

Response: This is a typographical error. It is suppressed.

Responses to Reviewer 2

The study is well designed with objectives, methodology and procedures well described. Good clinical practice guidelines are followed and risk and safety assessments have been considered.

Response: Thank you for your positive comment.

Please consider the following for the Introduction section. The authors only describe a small amount of studies on EC as an aid to quit smoking.

Response: We only considered randomised controlled studies of sufficient power. At the time of the writing of the protocol there was only two. On January 30th, 2019 was published the 3rd randomised controlled study: Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ.A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy.N Engl J Med. 2019 Feb 14;380(7):629-637. doi: 10.1056/NEJMoa1808779. Epub 2019 Jan 30. We now added some sentences about this paper in the Introduction, page 7.

A discussion on harm reduction approach would strengthen the introduction and provides a stronger rationale for the study.

Response: Being this a protocol, we have to focus on the current knowledge about efficacy trials and avoid all discussions e.g. about harm reduction because, as of today, i) there are no evidence based data about electronic cigarette's use associated harm reduction; this remains a hypothesis to confirm. ii) Our trial is not intended/was not conceived to assess harm reduction so our discussion would be out of the scope of this study.

Furthermore, discussion on safety of EC should be addressed.

Response: Available safety data, serious adverse events, from randomised controlled studies have already been mentioned on page 7. We now added safety data from the Hajek et al. 2019 study. One of the main objectives of this trial is recording and reporting convincingly safety data but we do not think that in this protocol we have to list all kinds of adverse effects coming from various type of studies.

Currently, the authors omits the controversies around ECs and should be in part acknowledged. For example, the authors state in the article "observational cohorts provided conflicting results as an aid to quit smoking and will not be mentioned further".

Response: Being this a protocol and not a review, we have to focus on the current knowledge about efficacy trials. Results of observational trials are difficult to compare to randomized, placebo controlled or reference drug controlled trials; comparative conclusions can be inadequate. Therefore, we decided not to report and discuss the controversial results of observational trials. However, we completed this sentence (page 7) "Observational studies provide lower level of evidence (for various reasons) than randomised, controlled, double blind trials, therefore results are difficult to compare adequately."

VERSION 2 – REVIEW

REVIEWER	Jamie Hartmann-Boyce University of Oxford, UK
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	Thank you very much for addressing my comments - I am happy with the responses. The manuscript would still benefit from a thorough copyedit as there are still some typos/grammatical errors but I assume the publisher will take care of this. I think the authors' treatment of the observational data is appropriate and appreciate that they have updated the text with results from Hajek et al. I have two minor amendments that I think would improve the manuscript: (1) It might be useful to add one further line to the intro re: Hajek to state that no serious adverse events that occurred in either arm were considered to be related to study treatment (otherwise it seems odd to just mention less serious AEs, and given many people have concerns about the safety profiles of electronic cigarettes it may be valuable to add this in). (2) It is great that the authors are planning to have input from their press office in terms of dissemination but this isn't really what I meant by patient and public involvement (by which I mean involving the public in the design and conduct of the research), so I might suggest amending the new sentence to "The Service Presse of Assistance publique-Hôpitaux de Paris will help prepare a dissemination plan to ensure results are accessible to the public."

VERSION 2 – AUTHOR RESPONSE

Responses to the comments of Reviewer 1.

Thank you for these further comments that will again improve the manuscript.

I am happy with the responses. The manuscript would still benefit from a thorough copyedit as there are still some typos/grammatical errors but I assume the publisher will take care of this. I think the authors' treatment of the observational data is appropriate and appreciate that they have updated the text with results from Hajek et al. I have two minor amendments that I think would improve the manuscript:

(1) It might be useful to add one further line to the intro re: Hajek to state that no serious adverse events that occurred in either arm were considered to be related to study treatment (otherwise it seems odd to just mention less serious AEs, and given many people have concerns about the safety profiles of electronic cigarettes it may be valuable to add this in).

Response: We added to the Introduction (page 7) as to Peter Hajek's paper "However, no serious adverse events occurred in either arm that were considered to be related to study treatment."

(2) It is great that the authors are planning to have input from their press office in terms of dissemination but this isn't really what I meant by patient and public involvement (by which I mean involving the public in the design and conduct of the research), so I might suggest amending the new sentence to "The Service Presse of Assistance publique-Hôpitaux de Paris will help prepare a dissemination plan to ensure results are accessible to the public."

Response: It is not (or not yet) usual in France to involve patients or other publics in the design and conduct of a clinical trial. Thank you for the sentence; we included it on page 22.