PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf)** and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effectiveness and safety of nicotine patches combined with e-cigarettes (with and without nicotine) for smoking cessation: Study protocol for a randomised controlled trial.
AUTHORS	Walker, N; Verbiest, Marjolein; Kurdziel, Tomasz; Laking, George; Laugesen, Murray; Parag, Varsha; Bullen, Chris

VERSION 1 – REVIEW

REVIEWER	Kenneth Perkins WPIC, Dept of Psychiatry, Univ of Pittsburgh, Pittsburgh, PA 15213, USA
REVIEW RETURNED	24-Apr-2018

GENERAL COMMENTS	Careful evaluation of the efficacy of ECigarettes for smoking cessation, alone or supplementing other treatment, is needed to guide clinical treatment advice. This description of the ASCEND-II protocol comprehensively presents the details of procedures to compare the efficacy of nicotine ECig vs placebo ECig vs no ECig among quitting smokers also using 21 mg NRT patch daily. Many strengths are apparent in this protocol, including very large study samples in order to ensure adequate power to detect relatively modest absolute differences in quit outcomes, as well as inclusion of weekly “support” calls to provide brief counseling to aid quit success in the first 6 weeks. Other positive elements include double-blind assignment of nicotine vs placebo ECig, starting patch and ECig use during 2 weeks leading up to TQD, and biochemical validation of quit status at 6 months post quit date (TQD). Questions are relatively minor and do not significantly detract from this well-designed clinical trial, but some issues may warrant further consideration when reporting and interpreting results. First, the primary outcome of “continuous abstinence” relies mostly on self-report of no (or minimal) smoking post-TQD plus CO<=10 ppm at just the 6 month followup point. Practical limitations in more frequent assessments of CO during and after the treatment period is understandable, but it would appear “continuous” abstinence can only be defined as “self-reported”, while CO at 6 months is “biochemically-confirmed point prevalence” abstinence. Second, CO<=10 ppm appears overly “generous” as verifying “abstinence”, since Bedfont monitors show CO<8 ppm when validating 24-hr abstinence. Moreover, “non-daily smokers” recruited here are very likely to show CO<10 on days PRIOR to their TQD, so using that cutoff for post-TQD “abstinence” does not appear valid. Third, virtually all the secondary measures will be via self-report at intermitted phone calls 1, 3, 6, and 12 months post-TQD, including

	body weight, time to relapse, compliance, etc., which will lead to questionable reliability of those self-reports. Fourth, how is “wanting to quit in the next two weeks” assessed in a way to ensure reliability/consistency of quit interest? If some change their mind after randomization but prior to their TQD, will they be counted as “not quit” in an “intent to treat” approach? Or not counted and replaced with other participants maintaining consistent high quit interest through the treatment period? Finally, the design appeared to focus statistical power on a less critical clinical question. The primary comparison between the large samples randomized to nicotine vs placebo ECig conditions (n=804 each) should certainly be able to address whether supplementing NRT patch with nicotine via ECig, vs simple ECig use behavior per se (i.e. placebo ECig), improves quit outcome. However, such an outcome would confirm that increasing the nicotine dose exposure aids outcome, which has generally been demonstrated (e.g. older trials of double patches or very high dose patch), and it’s not clear that advising supplemental use of ECigs specifically containing nicotine rather than placebo is a critical question. More clinically relevant would appear to be showing that the addition of nicotine (or any) ECig use increases quit outcomes beyond the NRT patch treatment alone (only n=201), the current modest intervention standard for NRT. If nicotine ECig is superior to no ECig among those also using NRT patch, results would warrant advising quitting smokers to use both products concurrently, as well as answering a key question in this clinical literature—can nicotine ECig independently aid quit outcome.

REVIEWER	Pasquale Caponnetto University of Catania
REVIEW RETURNED	12-May-2018

GENERAL COMMENTS	Secondary outcomes in abstract section is a little bit confusing, please reword more clearly. How will be assessed the motivation to quit? Eligibility Criteria: is not clear if people with other medical problem could be enrolled (eg diabetes, serious mental illness, COPD ....) Study interventions and procedures: Please explain the rationale about 14wk as treatment phase. Dual use (all time points): the definition of dual use is not clear. Is typical for people who smoke and vape and not for possible triple use, NRT,Ecig, Cigarette General health (all time points): Self-reported shortness of breath, cough, asthma, COPD, and mental health problems; I think that this information should be assessed by physician for physical problem and clinical psychologist for mental health problems

VERSION 1 – AUTHOR RESPONSE

Response to reviewer’s comments

Editorial Requirements:

1. Please include a completed copy of the SPIRIT checklist rather than CONSORT. SPIRIT is designed to improve the reporting of trial protocols. The full checklist can be found at: http://www.spiritstatement.org
This checklist has been uploaded, and the paper edited to ensure all aspects from the guideline are addressed

Reviewer: 1
2. The primary outcome of "continuous abstinence" relies mostly on self-report of no (or minimal) smoking post-TQD plus CO<=10 ppm at just the 6 month follow-up point. Practical limitations in more frequent assessments of CO during and after the treatment period is understandable, but it would appear "continuous" abstinence can only be defined as "self-reported", while CO at 6 months is "biochemically-confirmed point prevalence" abstinence.
The primary outcome is defined according to the 'Russell Standard' proposed by West et al in 2015. (reference 21 in the paper). This outcome is widely used in the tobacco control field, and considered by many researchers as the gold standard for defining smoking abstinence. Our paper clearly outlines the rationale for the definition. However, we conclude that, despite the limitations of the outcome (based on the point prevalence issue raised by the reviewer) and given the practical limitations of undertaking CO measures, the outcome is the best that can be achieved.

3. Second, CO<=10 ppm appears overly "generous" as verifying "abstinence", since Bedfont monitors show CO<8 ppm when validating 24-hr abstinence. Moreover, "non-daily smokers" recruited here are very likely to show CO<10 on days PRIOR to their TQD, so using that cutoff for post-TQD "abstinence" does not appear valid.
a. There was an error in our paper. The 'Russell Standard' proposes using a CO measure of ≤9 ppm. Our paper has been updated accordingly.
b. We acknowledge that the best CO cut-off to use in research studies is debated by many researchers. For this reason we plan to undertaken sensitivity analysis using different CO cut-offs (see page 15), including for non-daily smokers.

3. Third, virtually all the secondary measures will be via self-report at intermitted phone calls 1, 3, 6, and 12 months post-TQD, including body weight, time to relapse, compliance, etc., which will lead to questionable reliability of those self-reports.
a. We acknowledge that self-report of outcomes could introduce bias into the trial. However randomisation ensures that any bias is balanced between the treatment arms.
b. This is trial was pragmatic in design, with participants distributed throughout the nation, and not seen face-to-face during the study. We do not have the resources, time, or funding to undertake in-person, face-to-face measures. (we had only NZ$600,000 [€352,000 or US$407,000] to undertake this study over a three year period.)

4. Fourth, how is "wanting to quit in the next two weeks" assessed in a way to ensure reliability/consistency of quit interest? If some change their mind after randomization but prior to their TQD, will they be counted as "not quit" in an "intent to treat" approach? Or not counted and replaced with other participants maintaining consistent high quit interest through the treatment period?
a. We simply ask potential participants if they want to quit in the next two weeks. We do not follow a 'Stages of change' model when assessing readiness to quit smoking. Instead we follow Robert West's PRIME theory of motivation which assumes motivation to quit is dynamic.
b. We adhere to the intention-to-treat principle for clinical trials, which requires that once a person is randomised they stay in the trial and are not 'replaced' with a new person.

5. Finally, the design appeared to focus statistical power on a less critical clinical question. The primary comparison between the large samples randomized to nicotine vs placebo ECig conditions

(n=804 each) should certainly be able to address whether supplementing NRT patch with nicotine via ECig, vs simple ECig use behavior per se (i.e. placebo ECig), improves quit outcome. However, such an outcome would confirm that increasing the nicotine dose exposure aids outcome, which has generally been demonstrated (e.g. older trials of double patches or very high dose patch), and it's not clear that advising supplemental use of ECigs specifically containing nicotine rather than placebo is a critical question.

a. We hypothesised that adding NRT to the nicotine e-cigarette would increase quit rates. We agree with the reviewer that this hypothesis is likely to be proven, based on efficacy trials of double patches and high dose patches.

b. However, although we know that increasing nicotine dose exposure improves quit rates, there are vital pharmacokinetic differences between transcutaneous sustained release nicotine products and inhaled nicotine products. We do not yet know the extent to which increased nicotine dose-exposure by inhalation aids outcome.

c. Furthermore, this trial investigates effectiveness (i.e. the real world use of the products), not efficacy (e.g. where participants are paid to be treatment compliant). The trial answers a real world question, directly relevant to policy decisions needing to be made by governments around the world who do not currently allow nicotine containing ecigarettes to be marketed or sold.

6. More clinically relevant would appear to be showing that the addition of nicotine (or any) ECig use increases quit outcomes beyond the NRT patch treatment alone (only n=201), the current modest intervention standard for NRT. If nicotine ECig is superior to no ECig among those also using NRT patch, results would warrant advising quitting smokers to use both products concurrently, as well as answering a key question in this clinical literature—can nicotine ECig independently aid quit outcome. We believe our secondary comparison is also of importance for the reasons highlighted by the reviewer. However, in our country, tobacco control policy makers were more interested in the first question.

Reviewer: 2

1. Secondary outcomes in abstract section is a little bit confusing, please reword more clearly.
This section has been reworded

2. How will be assessed the motivation to quit?
We simply ask potential participants if they want to quit in the next two weeks.

3. Eligibility Criteria: is not clear if people with other medical problem could be enrolled (e.g. diabetes, serious mental illness, COPD ....)

a. People with other medical conditions are eligible to enrol in the trial as stated in paragraph one on page 8.

b. This trial takes a pragmatic approach with open eligibility, in an effort to ensure the study findings are generalizable to as many people as possible in the population.

4. Study interventions and procedures: Please explain the rationale about 14wk as treatment phase.

a. Standard treatment in New Zeakand for NRT and other smoking cessation medication is 12 weeks. For this reason 12 weeks was chosen, but a 2 week pre-quit period was added to allow participants time to familarise themselves with the e-cigarettes.

b. A 12 week post-quit treatment period also allows the trial to be compared to the other two e-cigarette trials outlined in Table 1.

5. Dual use (all time points): the definition of dual use is not clear. Is typical for people who smoke and vape and not for possible triple use, NRT,Ecig, Cigarette.

a. Dual use is defined as “daily use of both their allocated e-cigarette and usual cigarettes”
b. This information has been added to the paper on page 11
6. General health (all time points): Self-reported shortness of breath, cough, asthma, COPD, and mental health problems; I think that this information should be assessed by physician for physical problem and clinical psychologist for mental health problems.
a. Whilst a physical examination and mental health assessment using detailed screening tools would be ideal, it is not possible for financial and logistical reasons. We will acknowledge this issue as a limitation of the study in the outcome paper.
b. This is a real-world, pragmatic trial. Participants are recruited from throughout the country and all data collection is undertaken over the phone. We could ask participants to attend a GP or a community-based clinic so that this information could be collected, but participants are unlikely to attend based on our previous research (even if we incentivise them – which we can’t, as we don’t have access to sufficient research funds).
c. We could also employ a doctor to collect this information over the phone, but again we do not have access to sufficient funds to pay a doctor to undertake this many assessments. Note, the ‘smoking cessation clinic’ model available in many countries around the world, does not exist in New Zealand.

VERSION 2 – REVIEW

REVIEWER	Kenneth Perkins Dept of Psychiatry, Univ of Pittsburgh, USA
REVIEW RETURNED	12-Jul-2018

GENERAL COMMENTS	This revised pragmatic study protocol is similar to the original, with details of procedures to compare the efficacy of nicotine ECig vs placebo ECig vs no ECig among quitting smokers also using 21 mg NRT patch daily. Strengths remain, such as the large study samples and inclusion of weekly “support” calls to provide brief counseling to aid quit success, and biochemical validation of quit status at 6 months post quit date (TQD). Yet, several limitations noted in evaluating the prior version remain, such as continued criterion of CO= 9 ppm (i.e. CO<10 ppm) as verifying “abstinence”, which will count as abstinent those who may have smoked in the last day. As noted previously, Bedfont monitors show CO<8 ppm provides optimum sensitivity when validating 24-hr abstinence. Also as previously noted, the “non-daily smokers” to also be recruited here are very likely to show CO<10 on nearly all days, even prior to their TQD, so using that cutoff for post-TQD “abstinence” is not valid. Assuming the actual reading will be recorded, analyses on “abstinence” should use a cutoff of <8 ppm. Second, little clarification was provided to specify how “wanting to quit in the next two weeks” will be assessed in a way to ensure reliability/consistency of quit interest. Especially among non-daily smokers, some may change their mind after randomization and a high number of dropouts could lessen the planned sample sizes, complicating power considerations in an “intent to treat” approach. Because this trial has apparently already been conducted, it's not clear if there might be data to determine lack of reliable desire to quit as a reason for any drop outs.

REVIEWER	Caponnetto, Pasquale Universita degli Studi di Catania Scuola di Facolta di Medicina
REVIEW RETURNED	28-Jul-2018

GENERAL COMMENTS	1) The authors needs to list strengths and weaknesses of ASCEND 2. 2) The authors needs to specify in the text why an Ascend 2 was necessary after Ascend. What Ascend 2 is adding to Ascend? 3) Limitation of RCTs to prove e-cigarette effectiveness should be discussed. 4) There are several typos in the text (e.g lack of space between words) 5) Introduction: please include something about psychological and social aspects related to smoke traditional cigarettes 6) It's again not clear as you evaluated motivation to quit 7) Include non daily smoking is questionable and give them e-cigarettes and could be a way to improve new addiction. I think that this aspect is interesting but should studied in a separate study and include in this study only daily smokers of at least 10 cigarettes day considering you give them nicotine patches and e-cig with nicotine. 8) page 9, please specify time from screening-information to consent form signature. 9) Please give a rationale about 14 and not 12 week of treatment 10) Please give more information about behavioral support

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

1. Use of CO=9 ppm (i.e. CO<10 ppm) as verifying “abstinence”, which will count as abstinent those who may have smoked in the last day. As noted previously, Bedfont monitors show CO<8 ppm provides optimum sensitivity when validating 24-hr abstinence.
    a. The trial has achieved data lock and the data have been analysed. As stated in the paper, we planned (and undertook) sensitivity analyses to determine the impact of using varying cut-offs for CO measurements, given a lack of consensus about the best reading to use. These cut-offs were ≤3ppm, ≤5ppm and ≤8ppm. This information has been added to the paper. Whilst the ≤8ppm cut-off does not match the reviewers request, we feel we have addressed the general issue (and do not feel it is necessary to undertake a post-hoc analysis for a CO<8 ppm).

2. Also as previously noted, the “non-daily smokers” to also be recruited here are very likely to show CO<10 on nearly all days, even prior to their TQD, so using that cut-off for post-TQD “abstinence” is not valid. Assuming the actual reading will be recorded, analyses on “abstinence” should use a cut-off of <8 ppm.
    a. See above point

3. Little clarification was provided to specify how “wanting to quit in the next two weeks” will be assessed in a way to ensure reliability/consistency of quit interest. Especially among non-daily smokers, some may change their mind after randomization and a high number of dropouts could lessen the planned sample sizes, complicating power considerations in an “intent to treat” approach. Because this trial has apparently already been conducted, it's not clear if there might be data to determine lack of reliable desire to quit as a reason for any drop outs.
    a. The question was “do you wish to set a quit date in the next 2 weeks – Yes or No’. The question was no more specific than that, and can’t be changed now that the trial has finished.

b. Smokers frequently change their minds about their intentions to quit. This fact highlights the importance of conducting pragmatic trials because they enable the 'real world' effectiveness of an intervention to be determined against this background of changes in motivation.
c. The point raised about drop-out has been addressed in the sample size calculation. A per protocol analysis will also be undertaken.

Reviewer: 2

1. The authors needs to list strengths and weaknesses of ASCEND 2.
    a. Page 3 has a specific section on strengths and limitations

2. The authors needs to specify in the text why an Ascend 2 was necessary after Ascend. What Ascend 2 is adding to Ascend?
    a. The two studies are unrelated. We have simply called the trial ASCEND-II as it was our second trial of e-cigarette for smoking cessation. To avoid confusion we have removed the trial name ('ASCEND-II') from the paper.

3. Limitation of RCTs to prove e-cigarette effectiveness should be discussed.
    a. A statement to address this issue has been added to Pages 15-16.

4. There are several typos in the text (e.g lack of space between words)
    a. We are unable to address this point as we can find no issues with 'space between words' or 'typos' in the paper. Perhaps the reviewer is confused with the European versus American spelling of some words?
5. Introduction: please include something about psychological and social aspects related to smoke traditional cigarettes.
    a. We believe this issue has been addressed in the first paragraph of the introduction (and referenced).

6. It's again not clear as you evaluated motivation to quit
    a. See answer to reviewer 1, question 3

7. Include non-daily smoking is questionable and give them e-cigarettes and could be a way to improve new addiction. I think that this aspect is interesting but should studied in a separate study and include in this study only daily smokers of at least 10 cigarettes day considering you give them nicotine patches and e-cig with nicotine.
    a. The trial has achieved data lock and the data have been analysed. We therefore can't address this issue.

8. page 9, please specify time from screening-information to consent form signature.
    a. These steps occur within the one phone call. This information has been added to Page 8

9. Please give a rationale about 14 and not 12 week of treatment
    a. This information is already in the paper and is referenced, however we have reordered the text on page 9 to make it clearer.

10. Please give more information about behavioral support
    a. More details has been added to page 9