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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 (ASCEND-II).

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ABSTRACT

Introduction: Epidemiological evidence indicates e-cigarettes can help people quit smoking, however more confirmatory trials are needed. To date, no trials have evaluated the effectiveness and safety of combining nicotine patches with second-generation e-cigarettes (with and without nicotine) for smoking cessation.

Methods and analysis: The ASCEND-II trial is pragmatic, three-arm, community-based, single-blind, randomised trial undertaken in New Zealand. Eligible participants are daily or non-daily smokers, aged ≥18 years, naive e-cigarette users, and motivated to quit smoking in the next two weeks. Participants are recruited using multi-media advertising. 1,809 participants will be randomised to 14 weeks of: 1) 21mg nicotine patches (n=201); 2) 21mg nicotine patches plus a 18mg/mL nicotine e-cigarette (n=804); or 3) 21mg nicotine patches plus a nicotine-free e-cigarette (n=804). Participants receive weekly withdrawal-oriented behavioural support calls for six weeks post-randomisation. The primary outcome is self-reported biochemically verified continuous abstinence at six months post quit-date. The primary comparison is nicotine patch + nicotine-free e-cigarette versus nicotine patch + nicotine e-cigarette, and the secondary comparison is nicotine patch alone versus nicotine patch + nicotine e-cigarette (90% power at p=0.05 to detect an absolute difference in six month continuous abstinence rates of 8% and 15% respectively). Secondary outcomes, collected by phone interview at quit date, then one, three, six and 12 months post quit date, include: self-reported continuous abstinence, 7-day point prevalence abstinence, cigarettes per day, smoking reduction, time to relapse, self-efficacy, use of other cessation support, side effects/serious adverse events, crossover, treatment compliance, additional e-cigarette support, dual use, treatment continuation, treatment perceptions and recommendations, and cost.

Ethics and dissemination: Ethics approval was obtained from the NZ Northern A Health and Disability Ethics Committee. Outcomes will be disseminated through publication, conference/meeting presentations, and media.

Trial registration number: ClinicalTrials.gov (NCT02521662)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first trial to investigate the effectiveness and safety of combining nicotine patches and e-cigarettes on smoking abstinence.
- This is the first large, pragmatic, community-based trial testing a second generation e-cigarette for smoking cessation, with choice of device and juice undertaken in consultation with members of the vaping industry.
- The trial includes both daily and non-daily smokers.
- The trial is undertaken in a country with strong tobacco control measures in place, and low uptake of e-cigarettes.
- For ethical reasons, in NZ it was not possible to include a fourth comparison group of placebo patches.

INTRODUCTION

Smoking cessation treatments should address at least two aspects of tobacco dependence: physiological and behavioural dependence.[1] Although nicotine replacement therapies (NRT) help address the physiological dependence of cigarette smoking by providing nicotine to the body, they don't mimic the habituated tactile behaviors (involving the mouth and hands) associated with cigarette use.[2]

Electronic cigarettes (e-cigarettes) have considerable potential to help people quit smoking as they address both the physiological and behavioural dependence of tobacco smoking.[3 4] These devices deliver nicotine by a form of aerosolisation (popularly known as vaping), and are likely safer to use than smoking tobacco as users have reduced exposure to tobacco toxicants.[5-10] To date, only two randomised trials with six-month abstinence outcomes have been published on the use of e-cigarettes for smoking cessation (Table 1).[11-13]

Table 1: Summary of the design and outcomes from the two published trials of e-cigarettes for smoking cessation

	ECLAT **Caponnetto et al 2013**[11]	**ASCEND** **Bullen et al 2013**[12 13]
Population	Unmotivated to quit	Motivated to quit
Eligibility	≥10 CPD for at least 5 years, 18-70 years	≥10 CPD for last year, ≥18 years
E-cigarette brand	Categoria (First generation)	Elusion (First generation)
Sample size	300 (1:1:1)	657 (4:4:1)
Intervention	7.2mg e-cigarette (n=100)** 7.2-5.4mg e-cigarette (n=100)** 0mg e-cigarette (n=100)** No behavioural support	16mg e-cigarette (n=289)** 21mg nicotine patch (n=295) 0mg e-cigarette (n=73)** Minimal behavioural support
Intervention period	12 weeks	13 weeks (includes one week pre-quit)
Follow-up	12 months	Six months

Power	75%	80%
Continuous abstinence at 6 months*	7.2 mg e-cigarette: 12% 7.2-5.4 mg e-cigarette: 10% 0 mg e-cigarette: 5% p=0.39	Nicotine e-cigarette: 7.3% Nicotine patches: 4.1% RD=1.51 95% CI −2.49-5.51 Nicotine e-cigarette: 7.3% Placebo e-cigarette: 5.8% RD=3.16 95% CI −2.29-8.61
Smoking reduction	**Percentage reduction in CPD at six months** 7.2 mg e-cigarette: 17% 7.2-5.4 mg e-cigarette: 19% 0 mg e-cigarette: 15% p=0.39	**Reduced CPD by ≥ 50% at six months** Nicotine e-cigarette: 57% Nicotine patches: 41% p=0.0002 Nicotine e-cigarette: 57% Placebo e-cigarette: 45% p=0.08
Time to relapse (median)	Not reported	Nicotine e-cigarette: 35 days Nicotine patches: 14 days Placebo e-cigarette: 12 days
Adverse events	No difference in frequency of events between groups at week 12 and 52	Nicotine e-cigarette: 137 events in 107 participants over six months. 0.8 events per person month Nicotine patches: 119 events in 96 participants over six months. 0.8 events per person month Placebo e-cigarette: 36 events in 26 participants over six months. 0.9 events per person month Nicotine e-cigarette vs Nicotine patches: IRR=1.05, 95% CI: 0.82-1.34, p=0.7
Serious adverse events	None reported	None related to treatment

*Primary Outcome
**_Ad libutum_ use
RD=Risk Difference
CI=Confidence Intervals
IRR=Incidence Rate Ratio
CPD=Cigarettes Per Day

In New Zealand (NZ), nicotine is regulated as a medicine, except when delivered in tobacco smoke. It is currently illegal to sell an e-cigarette that contains nicotine or to make a cessation claim about e-cigarettes, because Medsafe (NZ's competent authority for licensing medicines) considers e-cigarettes a medicine if a cessation claim is made, or when supplied with nicotine. The case for maintaining the status quo in NZ (i.e. only nicotine-free e-cigarettes available for sale) is that the efficacy of e-cigarettes is largely due to their behavioural replacement for conventional cigarettes. Indeed, some studies report a reduction in cravings to smoke with nicotine-free e-cigarettes,[12 13] and point to some degree of support for cessation. If an e-cigarette user in NZ wants to have nicotine, they can combine the use of an e-cigarette with NRT (which are medically approved nicotine products). However, to date no trial has investigated the impact of combining NRT and e-cigarettes on smoking abstinence. There is good evidence that combining NRT products (e.g. slow acting nicotine patches combined with faster-acting oral products, such as lozenges, gum or mouth spray) is more effective than monotherapy alone, and as safe.[14]

We designed a clinical trial to assess the effectiveness, acceptability, utilisation and safety of combining 21mg nicotine patches with e-cigarettes (with and without nicotine) on smoking abstinence at six months. Our primary hypothesis is that 21mg nicotine patches plus 18 mg/mL nicotine e-cigarettes will be more effective at helping smokers quit than 21mg nicotine patches plus nicotine-free e-cigarettes. Our secondary hypothesis is that combination therapy (i.e. 21mg nicotine patches plus 18 mg/mL nicotine e-cigarettes) will be more effective than monotherapy (i.e. 21mg nicotine patches alone).

METHODS AND ANALYSIS

Choice of design and intervention

A three-arm, randomised-controlled, parallel group design is used to answer the research question. Whilst it is logical to include a fourth group (i.e. placebo patches), it is unethical in NZ to deny a smoker access to a proven smoking cessation medication. For this reason, only an active nicotine patch is used. A 21mg (24 hour) nicotine patch was selected as it is the standard patch strength used in NZ (Habitrol® 21mg patch, distributed in NZ by Novartis Consumer Health Australasia Pty. Ltd.). A second generation e-cigarette starter kit (eVOD brand, 1.8 OHM: Kangertech, Shenzhen GuangDong, China) was chosen for the trial, with an 18mg/mL nicotine strength. Each kit contains two batteries, two cartridges, two charging kits, one carry case, and five atomisers. Participants can choose one of two tobacco flavours for their e-juice, based on the type of tobacco they usually smoke (i.e. roll-your-own or factory. Approximately 38% of NZ smokers use roll-your-own tobacco exclusively[15]). The e-

liquid (60/40 PG/VG ratio) used in the trial is sourced from Nicopharm, an Australian-based compounding pharmacy producing pharmaceutical grade e-juice under Good Manufacturing Standards (https://www.nicopharm.com.au/). The e-juice will be independently assessed to verify nicotine content is as labeled, and to check for contaminants. For the nicotine e-liquid, a variability of +/- 10% nicotine concentration will be considered acceptable. Batch-to-batch variability of nicotine content in the e-liquid will also be assessed.

Patient and public involvement

Smokers and members of the public were not involved in the development of the research question or study design, and are not involved in recruitment or trial conduct. Choice of outcome measures was not directly informed by smokers' priorities, experience, or preferences, nor has the burden of the intervention been assessed by smokers. However, the brand and type of e-cigarette, nicotine strength for the e-juice, and choice of flavours was selected based on advice received from members of the NZ vaping retailer community. A summary of the study results will be posted/emailed to all trial participants.

Study population

People who smoke cigarettes, currently live in NZ, are motivated to quit within the next two weeks, and meet the eligibility criteria outlined below. Both daily and non-daily smokers are included in the trial. We have chosen to include non-daily smokers, given the NZ environment of limited research funding, a drive to reach NZ's smokefree2025 goal, and unpublished data from the NZ Health Survey showing an increase in the number of non-daily smokers (from 7.7% in 2006/07, to 9.3% in 2012/13) who are less likely to be asked about their smoking habits by their GP, suggesting they are less likely to receive cessation support. The risk versus benefit analysis of including this population in the trial considered the harms of continued smoking (and high likelihood of receiving no cessation support) versus the potential risk of exposure to higher than normal nicotine levels via the trial interventions (acknowledging that users will self-titrate).

Eligibility criteria

Participants will be eligible if they are: at least 18 years of age, able to provide verbal consent, have access to a telephone, and prepared to use the trial treatments. Only one person per household is eligible. There is no language restriction for participation in the trial, as translation services will be available if required. Women who self-report that they are pregnant or breastfeeding will be excluded from the trial, as will current users of NRT, people currently enrolled in another smoking cessation programme or cessation study, people who have used an e-cigarette for smoking cessation for more than one week anytime in the last

year, or current users of non-nicotine based cessation therapies (e.g. buproprion, clonidine, nortriptyline or varenicline). People are also ineligible if they have any contraindications to nicotine patches (i.e. they have had a heart attack, stroke or severe angina within the previous two weeks, as per recommendations by the NZ Quitline) or e-cigarette (i.e. they self-report a history of severe allergies and/or poorly controlled asthma). There are no other exclusion criteria - as a pragmatic trial all people who smoke are eligible for the trial, irrespective of their medical/psychiatric history.

Recruitment

Potential participants will be recruited via community-based advertising, media advertising and social media. People interested in the trial will be directed to contact the study centre at the University of Auckland's National Institute for Health Innovation (NIHI) by freephone, email, Facebook or through the study website.

Randomisation, allocation concealment and sequence generation

People who register their interest in the study will be phoned by a research assistant and provided with further information about the study. A two-step verbal consent process will be used, where permission will be sought from participants to 1) undertake screening, and 2) undertake randomisation. A copy of the patient information sheet and electronic consent form will be posted/emailed to participants for their records. After screening, baseline data will be collected and participants will be allocated to one of the three study groups in a 1:4:4 ratio (21mg nicotine patch alone: 21mg nicotine patch plus 18mg/mL nicotine e-cigarette: 21mg nicotine patch plus nicotine-free e-cigarette) using stratified block randomisation (block size of nine). Randomisation will be stratified by ethnicity (Māori, non-Māori) to ensure an equal balance in this key prognostic factor. The randomisation sequence will be prepared by the study statistician.

Blinding

Participants and all research staff (except the project manager) are blinded to the nicotine content of the e-juice, until after data lock. The project manager is not involved in any data collection or interaction with trial participants. The e-juice is stored in a brown bottle.

Study interventions and procedures

Participants will be randomised to one of three treatment arms:

- 14 weeks of 21mg nicotine patch alone (n=201)
- 14 weeks of 21mg nicotine patch plus 18mg/mL nicotine e-cigarette (n=804)

- 14 weeks of 21mg nicotine patch plus nicotine-free e-cigarette (n=804)

At the time of randomisation participants in all three arms will receive 10-15 minutes of telephone-based withdrawal-oriented behavioural support and advice on using their allocated product. All three groups will also receive weekly withdrawal-oriented behavioural support telephone calls (10-15 minutes) for six weeks post-randomisation, delivered by trained smoking cessation advisors. A research assistant will courier participants 14 weeks supply of nicotine patches plus, if allocated, their e-cigarette and a 14 week supply of e-juice (four 30mL bottles). All products are supplied at no cost to participants.

Pre-quit period: At the time of randomisation, all participants will be advised to start using their nicotine patch (one patch per day) two weeks before their designated quit date. During this 'pre-quit' period, those participants randomised to receive an e-cigarette will also be advised to start using their device *ad libitum* in order to familiarise themselves with use of the e-cigarette.[12 13 16 17] Participants will be provided with written instructions on how to assemble and use their e-cigarette, plus provided with a web-link to 1) a NZ vaping industry designed document entitled "A Beginners Guide to Vaping" and 2) short on-line instruction videos hosted by a NZ-based on-line vaping retailer. This retailer will also provide a helpline number for participants to call should they need additional help or advice regarding use of the e-cigarette. The videos and helpline reflects 'real world' support offered by the vaping community in NZ for naive e-cigarette users (with the exception that no face-to-face support will be offered, although participants are free to choose to visit a vape shop and/or talk with a vaper at any time during the trial if they wish).

Intervention period: All participants will be instructed to stop smoking tobacco cigarettes from their designated quit date forwards, and continue with their allocated treatment for twelve weeks irrespective of any lapses back to smoking. All participants who have not quit by the end of follow-up will be provided with further cessation support within the context of publicly available cessation services in NZ.

Baseline assessments

The following baseline data will be collected via a phone interview with all participants:

- *Demographics*: Date of birth, gender, ethnicity, self-reported height and weight, and socio-economic position (based on education);
- *Smoking history:* Frequency of smoking (daily or non-daily, and if the latter – with what frequency), age when started, number of cigarettes smoked per day (or when smoking,

for non-daily smokers), number of years smoking, number of previous attempts to give up in past 12 months (including the longest time they stayed quit and the method used), type of cigarettes smoked per day (e.g. roll-your-own or factory-made), pack size, and how long each pack lasts, and whether they had tried to reduce the number of cigarettes smoked in the last 12 months;

- *Level of cigarette dependence:* Measured using the Fagerström Test for Cigarette Dependence;[18 19]
- *Other smoking related information*: Self-rated chances of quitting measured on a scale from 1 to 5 where 1= unlikely and 5= highly likely; smoking and e-cigarette use in the household; exposure to others who use e-cigarettes; smokefree home and car policies.
- *General health*: Self-reported shortness of breath, cough, asthma, Chronic Obstructive Pulmonary Disease (COPD), and current or history of mental health problems;
- *The physical signs and symptoms associated with withdrawal*: Measured using the Mood and Physical Symptoms Scale (MPSS),[20] including urge to smoke;
- *Concomitant medication*: Information about types of medication currently used.

Primary outcomes

The primary outcome will be self-reported biochemically verified (exhaled carbon monoxide-CO) continuous abstinence at six months post quit date. Continuous abstinence is defined according to the Russell Standard, i.e. self-report of smoking not more than five cigarettes from the quit date, supported by biochemical validation via exhaled breath CO measurement.[21] CO measurements will only be undertaken at the six and 12 month time point, and will be undertaken face-to-face by a researcher or community-based cessation provider at a site convenient to the participant. A CO Monitor (Bedfont Smokerlyzer; Bedfont Scientific Ltd, Station Road, Harrietsham, Maidstone, Kent, ME17 1JA, England) will be used, with a reading of ≤10 ppm signifying abstinence.[21]

Secondary outcomes

The following secondary outcomes will be assessed via a phone interview with participants on their designated quit date, and at one, three, six and 12 months after their quit date (Table 2).

- *Continuous abstinence (1, 3 and 12 months)*: The proportion of participants that have stopped smoking, defined as self-report of smoking not more than five cigarettes from the quit date;

Table 2: Details of follow-up

	Call 1			Call 2	Call 3	Call 4	Call 5	Call 6
Timing	**Week 0**			**Quit date (QD)**	**One month after QD**	**Three months after QD**	**Six months After QD**	**12 months After QD**
Description	**Screening (S), Baseline (B), Randomisation (R)**			**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**
General data								
Eligibility criteria	X							
Consent	X							
Age and gender		X						
Height		X						
Weight		X				X	X	X
Ethnicity		X						
Education		X						
Current medication		X		X	X	X	X	X
General health		X		X	X	X	X	X
Pregnancy	X			X	X	X		
Smoking information								
Level of nicotine dependence		X						
Type of tobacco smoked		X						
Pouch size and how long lasts^		X						
Cigarettes smoked per day		X		X	X	X	X	X
Age started		X						
Years smoked		X						
Household smoking		X						
Around others that use e-cigarettes		X				X		
Previous quit attempts & method		X						
Chances of quitting/effectiveness		X		X				
Any smoking in last seven days				X	X	X	X	X
Any smoking since QD					X	X	X	X
Biochemical verification in those who self-report quitting							X	X
Withdrawal/urge to smoke		X		X	X	X	X	X
Follow-up details								
Quit date			X	X				
Contact details			X	X	X	X	X	X
Treatment allocation and details			X					
Use of non-NRT cessation methods								
Type of cessation method used					X	X	X	X
Intervention period								
Acceptability / perceptions					X	X	X	X
Recommendations					X	X	X	X
Medication compliance				X	X	X		
Other outcomes								
Crossover				X	X	X	X	X
Additional e-cigarette support*				X	X	X	X	X
Dual use				X	X	X	X	X
Cost				X	X	X	X	X
Continuation of allocated treatment							X	X
Side effects/serious adverse events				X	X	X	X	X
Identity*						X	X	X

^ *In people who smoke roll-your-own tobacco* QD *Quit Date* * *In those allocated e-cigarettes*

- *7-day point prevalence (all time points):* The proportion of participants that have stopped smoking, defined as self-report of having smoked no cigarettes (not even a puff) in the past seven days;
- *Change from baseline in the number of cigarettes smoked per day, or when smoking for non-daily smokers (all time points):* If the participant is still smoking;
- *Proportion of participants who have significantly reduced smoking (all time points):* Percentage reduction, as well as the proportion who have reduced the number of cigarettes smoked (per day, or when smoking for non-daily smokers) by at least 50% (in order to allow comparison with data in the ASCEND trial[12 13]).
- *Time to first relapse from quit date:* Defined as return to daily smoking (for daily smokers);
- *Use of any other smoking cessation methods (all time points);*
- *Medication compliance (quit day, 1 and 3 months):* Participants will be asked whether they used their allocated product(s), and if not, why not. Participants who did use their allocated products(s) will be asked when they last used them, and how many days in the last week. Those allocated e-cigarettes will be asked how many mls of juice they use on a typical day (the EVod holds 2.2 mls).
- *Crossover (all time points):* Participants in the patch only group will be asked whether they accessed and used an e-cigarette (with or without nicotine) during the trial, and if so, at what time during the trial;
- *Weight (3, 6 and 12 months):* Self-reported;
- *Change from baseline in the physical signs and symptoms associated with withdrawal (all time points):* Measured using the MPSS,[20] including urge to smoke;
- *General vaping questions (all time points):* Urge to vape, whether they changed devices and/or e-juice; whether they accessed any support for using their e-cigarette (and if so, where and how useful the support was); whether anyone they see at least once a week currently uses an e-cigarette (including whether this is someone they live with or not);
- *Dual use (all time points):* Defined as 'daily use of both their allocated treatment and cigarettes';
- *Continuation of use (6 and 12 months):* Continued use of their allocated treatment after the end of the treatment period;
- *General health (all time points)*: Self-reported shortness of breath, cough, asthma, COPD, and mental health problems;
- *Self-rated chances of quitting (quit date):* measured on a scale from 1 to 5 where 1= unlikely and 5= highly likely;

- *Identity (3 and 6 months)*: Whether those allocated e-cigarettes consider themselves a smoker, a smoker still trying to quit, an ex-smoker, an ex-vapor, a vapor trying to quit smoking, a vapor trying to quit vaping, a vapor, other, or none of the above.
- *Perception of their product (1, 3, 6 and 12 months):* Participants' views on use of their allocated treatment as a smoking cessation aid;
- *Recommendations for use (1, 3, 6 and 12 months):* Whether they would recommend their allocated treatment to another smoker who wanted to quit;
- *Occurrence of specific side effects from product use (all time points);* Cough, nausea, dry mouth / throat, redness / swelling at patch site, dizziness, headache, vivid dreams, difficulty sleeping, dry skin, itchiness, other.
- *Serious adverse events (all time points);* Serious adverse events will be recorded and described as per International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, and followed to resolution or stabilisation.
- *Concomitant medication (all time points)*;
- *Cost information:* Cost per quitter, cost per person reducing their daily cigarette consumption (or when smoking for non-daily smokers) and the incremental cost effectiveness ratio, if the intervention is indeed shown to be more effective than the comparison condition. The tobacco expenditure savings to individual smokers will also be calculated using data on the amount smoked prior to quitting and the price of the particular products smoked.

Sample size

To detect an absolute difference of 8% in six-month continuous abstinence rates between the 21mg nicotine patch plus nicotine e-cigarette group and the 21mg nicotine patch plus nicotine-free e-cigarette group a sample size of 804 is needed in each group for 90% power (and 600 for 80% power). To detect an absolute difference of 15% in six month continuous abstinence rates between the 21mg nicotine patch alone group and the 21mg nicotine patch plus nicotine e-cigarette group a sample size of 201 is needed in each group for 90% power (and 150 for 80% power). A total sample size of 1,809 (804 in both e-cigarette groups and 201 in the nicotine patch only group) is needed for 90% power (Figure 1). The sample sizes are adjusted for 20% loss to follow-up (as per our previous e-cigarette trial[12]), and based on p=0.05 (2-sided).

<insert Figure 1 here>

A six month quit rate of 16% was assumed for the nicotine patch group, based on the average quit rate observed in trials of nicotine patches vs placebo/no NRT control included in a Cochrane review.[14] We estimated a six month quit rate of 31% for the nicotine patch plus nicotine e-cigarette group based on the quit rate observed in a trial (n=239) comparing 'nicotine patches plus nicotine spray' against 'nicotine patches plus placebo spray'.[22] A six month quit rate of 23% for the nicotine patch plus nicotine-free e-cigarette group was assumed, based on a pragmatic trial (n=1410) undertaken in NZ comparing use of NRT combined with very low nicotine cigarettes.[23] Our previous experience of recruiting smokers from the community suggests recruitment will take 18 months.[12]

Data management

Study data will be collected and managed using REDCap.[24] The study will be monitored early on during the study (after ten participants have been randomised), at study close-out and twice during the course of the trial. According to the guidelines proposed by Ellenburg et al. (2002) a Data Safety and Monitoring Committee is not required for this trial.[25]

Statistical analysis

Statistical analyses will be performed using SAS (9.4) and R.[26] No interim analyses are planned. Analysis will be carried out on an intention-to-treat basis (i.e. all participants as originally allocated after randomisation will be analysed, and all participants lost to follow-up will be assumed to be smoking), with the quit rates, relative risks (RR), absolute risks and 95% CI calculated for the primary and secondary comparison. Treatment groups will be compared using χ^2 tests, with multiple logistic regression analysis adjusting for other variables as appropriate. Sensitivity analyses will be undertaken to determine the impact of using varying cut-offs for CO measurements (given lack of consensus about the best reading to use), and secondary analyses performed to correct overall cessation rates for discordance between reported and verified cessation. Sensitivity analyses will also be carried out to determine the effect of missing data. If the level of missing data is deemed high (i.e. >20%) use of multiple imputation will be employed.[27] A per-protocol analysis will also be performed for the primary outcome where only those participants who completed the treatment originally allocated will be included (i.e. participants with major protocol violations, such as cross-overs treatments, withdrawals, and loss to follow-up will be excluded). The consistency of effects for pre-specified subgroups will be assessed using tests for heterogeneity. Subgroups will be based on age, sex, ethnicity, education, level of nicotine dependence, smoking frequency at baseline (daily/non-daily), and self-efficacy of quitting. Data related to smoking reduction will be reported separately for daily and non-daily smokers. A repeated measures model will be

used to analyse change from baseline in cigarettes smoked per day (in non-abstainers), and will adjust for baseline value. Kaplan-Meier curves, the log rank test, and Cox proportional hazards regression analysis will be used to analyse time-to-relapse. Serious adverse events will be defined according to the ICH-GCP E6 guidelines, categorised by the study doctor (masked to intervention product) as definitely, probably, possibly, unlikely, or not related to the intervention, and coded by a medical coder (masked to intervention product) according to ICD-10 AM (8th edition). Events will be analysed by treatment group and association with study treatment. If the primary outcome of the trial is positive analyses will be undertaken to model the marginal cost per quitter, taking a health sector perspective. The tobacco expenditure savings to individual smokers will also be calculated (for those who quit and cut down) to give a more societal perspective on the financial benefits (especially to low-income smokers). For those participants who cut down their tobacco consumption by a significant margin (i.e. ≥50%), the cost per person reducing their daily cigarette consumption will be calculated.

ETHICS AND DISSEMINATION

Ethics approval for the trial was obtained on the 16/09/2015 from the NZ Northern A Health and Disability Ethics Committee (15/NTA/123). Approval from the NZ Standing Committee on Therapeutic Trials was obtained on the 28/09/2015 for the use of e-cigarettes with nicotine. This study is registered with ClinicalTrials.gov (NCT02521662). The ASCEND-II dataset will be available from the corresponding author for use in any meta-analyses, on reasonable request. The dissemination plan includes national/international media coverage, publication in a high-impact peer-reviewed journal, and oral presentations to relevant national and international audiences (including government agencies).

DISCUSSION

The ASCEND-II trial is pragmatic in design and looks at the effectiveness of the trial interventions (as opposed to a more tightly controlled explanatory trial looking at efficacy), enabling the findings to be generalised to the unique tobacco control environment of NZ. Tobacco control measures have been implemented in NZ for the past 30 years. As a result tobacco is expensive (NZ$25.30, US$18.20, €15.44 as 24/08/17 for a pack of 20 cigarettes), tobacco advertising is banned, point of sale display bans are in effect, and cessation support and medication (including combination NRT) is accessible and heavily subsidised. Despite these measures, in 2015 16% of the NZ adult population (≥15 years) were current smokers (14% daily), including 39% of Māori[28] (indigenous NZers who comprise 15% of the population[29]) and 25% of Pacific people[28] (who comprise 5% of the population[29]). Within this

environment, e-cigarette usage in NZ is increasing. In 2011/12, a survey of 480 adults (≥ 18 years, smokers and recent quitters) found that 7% had ever purchased e-cigarettes.[30] In 2016, a survey of 3,854 NZ adults (>15 years old, smokers and non-smokers) reported 17% had tried an e-cigarette and 2% were current users (defined as: used at least daily, weekly or monthly).[31]

As a way to explain the pragmatic nature of the ASCEND-II trial, we have used a PRECIS-2 (PRagmatic-Explanatory Continuum Indicator Summary-2) wheel as a visual tool for readers.[32] The wheel has nine spokes (or domains) which focus on each aspect of the trial, namely: 1) eligibility, 2) recruitment, 3) setting, 4) organisation, 5) flexibility (delivery of the intervention), 6) flexibility (adherence to the intervention), 7) follow-up, 8) primary outcome, and 9) primary analysis. Each domain is scored on a 5-point Likert scale ranging from 1 "very explanatory" to 5 "very pragmatic". More pragmatic trials have a bigger wheel, whilst more explanatory trials have a smaller wheel. However, the tool also allows the reader to see that certain aspects of a trial may vary along the pragmatic to explanatory continuum. Five authors (NW, MV, TK, VP and CB) independently assessed the design according to the nine domains and the average scores for each domain are marked on each spoke in Figure 2 (with the range in scores shown in brackets).

<Insert Figure 2 here>

Current status

Recruitment started on 16th March 2016, with final data collection expected to be completed by July 2018. In March 2017 (almost two years after the ASCEND-II trial was designed and funded), the NZ Ministry of Health announced plans to "legalise the sale and supply of nicotine e-cigarettes and e-liquid as consumer products" from late 2018. The protocol was amended in April 2017, driven by the need to shorten the interview time, reduce participant burden and ensure the trial can finish on budget and on time. The amendments involved removal of the 12-month assessment and several non-essential secondary outcomes, namely: smokefree cars/homes (baseline); self-efficacy (one month); MPSS and urge to smoke (all time points); general vape questions (all time points); general health questions (quit date, one month); and perceptions of their allocated product and recommendations for use (one and six months). Details on the subset of participants that provided data on the secondary outcomes that were removed, will be published.

AUTHORS' CONTRIBUTIONS

NW, VP, GL, ML and CB conceived the original idea for the trial, sought and obtained funding for the trial, and wrote the study protocol. TK is the project manager responsible for the day-to-day running of the trial, whilst MV is the research fellow involved in the trial. VP will undertake all data analyses. This protocol paper was written by MV and NW with input from all co-authors. NW is guarantor for this paper. All authors read and approved the final manuscript.

FUNDING STATEMENT

This trial is funded by a three year project grant from the Health Research Council of NZ (15/202). The e-cigarettes for this trial are being purchased directly from NZVAPOR. NZVAPOR are not involved in the design, conduct or analysis of the trial, but are providing on-line and phone support to participants regarding use of their allocated e-cigarettes. The e-cigarettes to be used in the trial and NZVAPOR (including the Managing Director) have no links with the tobacco industry. The e-juice for this trial was purchased directly from Nicopharm, Australia. The nicotine patches are supplied by the NZ Government via their contract with Novartis. Nicopharm and Novartis are not involved in the design, conduct or analysis of the trial and have no known links with the tobacco industry. Independent testing of the nicotine content of the e-juice will be undertaken by the NicoTar group at Roswell Park Cancer Institute, Buffalo, New York, USA.

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We would like to thank members of the NZ vaping retailer community for their advice regarding the best type/brand of e-cigarette to use in this trial, plus the best nicotine strength and flavours for the e-juice. We also acknowledge the support of the funder, NZVAPOR, Nicopharm, Dr Maciej Goniewicz, and community smoking cessation providers throughout NZ.

COMPETING INTERESTS STATEMENT

No authors have received financial support for the submitted work from any companies with a financial interest in the products under investigation. CB has previously undertaken research funded by NicoNovum prior to its sale to RJ Reynolds. CB has received benefits in kind (accommodation expenses) from a manufacturer of smoking cessation medications. NW has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation medications. NW, CB, MV, GL and VP are

currently involved in a clinical trial in which varenicline and matching placebo are supplied by Pfizer under their Investigator-Initiated Research Program. MV has previously undertaken research supported by an unrestricted grant from Pfizer. None of the authors' spouses, partners, or children have financial relationships that may be relevant to the submitted work. All authors have no non-financial interests that may be relevant to the submitted work

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Figure 1: Estimated effect sizes for planned comparisons

Figure 2. Design of the trial along the 'pragmatic to explanatory' continuum

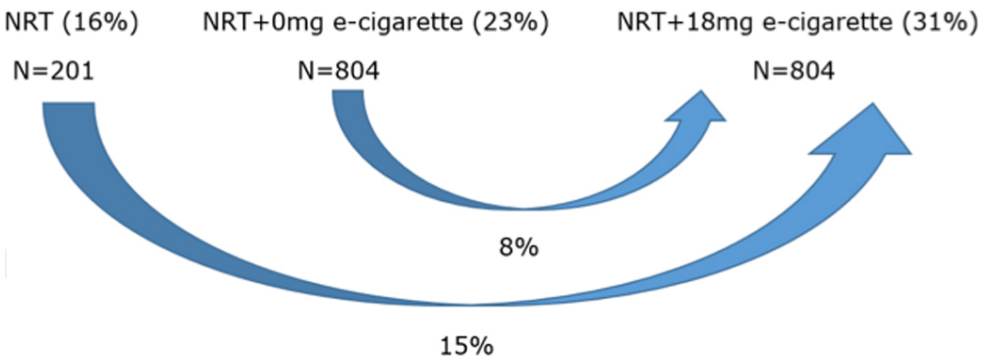

Figure 1: Estimated effect sizes for planned comparisons

375x375mm (72 x 72 DPI)

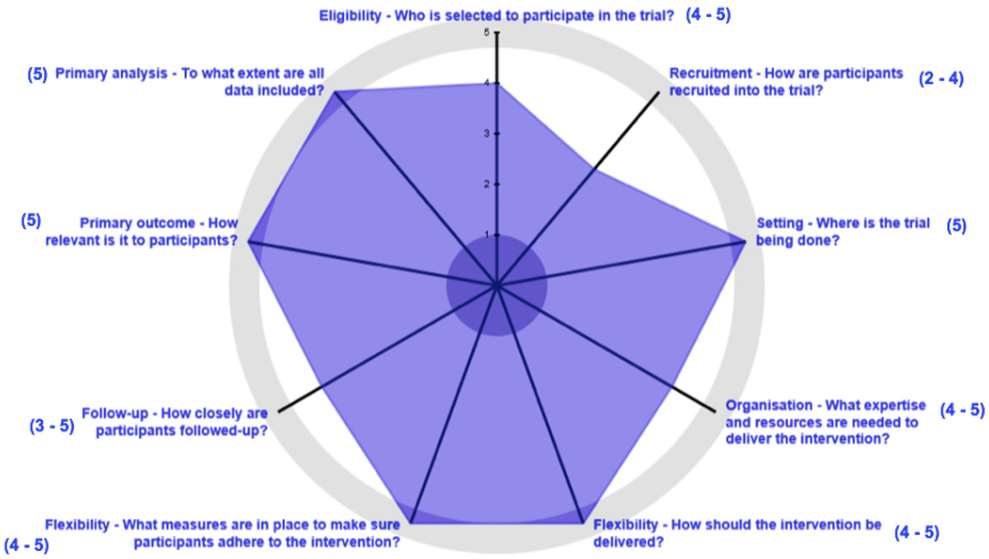

Figure 2. Design of the trial along the 'pragmatic to explanatory' continuum

375x375mm (72 x 72 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6, 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	16-17
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	16-17
Sample size	7a	How sample size was determined	13-14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	14-15
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14-15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n.a.
	13b	For each group, losses and exclusions after randomisation, together with reasons	n.a.
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n.a.
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n.a.
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n.a.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n.a.
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n.a.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n.a.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n.a.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n.a.
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n.a.
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n.a.
Other information			
Registration	23	Registration number and name of trial registry	2, 15
Protocol	24	Where the full trial protocol can be accessed, if available	n.a.
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

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 (ASCEND-II).

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Manuscript ID	bmjopen-2018-023659.R1
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Date Submitted by the Author:	12-Jul-2018
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Smoking and tobacco, Addiction, Research methods
Keywords:	e-cigarettes, nicotine patch, Clinical trial, smoking cessation, effectiveness, safety

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 (ASCEND-II).

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Running head: E-cigarettes and patches for smoking cessation

Word count (abstract): 298

Word count (paper): 4000

Keywords: Electronic cigarettes, E-cigarettes, Cessation, Nicotine Patch, Effectiveness, Safety, Randomised controlled trial.

ABSTRACT

Introduction: Evidence indicates e-cigarettes can help people quit smoking, however more confirmatory trials are needed. To date, no trials have evaluated the effectiveness and safety of combining nicotine patches with e-cigarettes (with and without nicotine) for smoking cessation.

Methods and analysis: ASCEND-II is a pragmatic, three-arm, community-based, single-blind, randomised trial undertaken in New Zealand. Eligible participants are daily/non-daily smokers, aged ≥18 years, naive e-cigarette users, and motivated to quit smoking in the next two weeks. Participants (n=1809) recruited using multi-media advertising, are randomised to 14 weeks of: 1) 21mg nicotine patches (n=201); 2) 21mg nicotine patches + 18mg/mL nicotine e-cigarette (n=804); or 3) 21mg nicotine patches + nicotine-free e-cigarette (n=804). Participants receive weekly withdrawal-oriented behavioural support calls for six weeks post-randomisation.

The primary outcome is self-reported biochemically verified continuous abstinence (CA) at six months post quit-date. The primary comparison is nicotine patch + nicotine-free e-cigarette versus nicotine patch + nicotine e-cigarette, and the secondary comparison is nicotine patch versus nicotine patch + nicotine e-cigarette (90% power, p=0.05, to detect an absolute difference in six-month CA rates of 8% and 15% respectively). Secondary outcomes, collected by phone interview at quit date, then one, three, six and 12 months post-quit date, include: self-reported CA, 7-day point prevalence abstinence, cigarettes per day (if smoking, or when smoking for non-daily smokers), time to relapse (if returned to smoking), belief in ability to quit, use of other cessation support, side effects/serious adverse events, treatment compliance, seeking additional support around e-cigarette use, daily use of both e-cigarettes and cigarettes, use of treatment past 14 weeks, views on treatment and recommendation to others, weight, and cost-per-quitter.

Ethics and dissemination: The Northern A Health and Disability Ethics Committee approved the trial. Findings will be disseminated through publication, conference/meeting presentations, and media.

Trial registration number: ClinicalTrials.gov (NCT02521662)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first trial to investigate the effectiveness and safety of combining nicotine patches and e-cigarettes on smoking abstinence.
- This is the first large, pragmatic, community-based trial testing a second generation e-cigarette for smoking cessation, with choice of device and juice undertaken in consultation with members of the vaping industry.
- The trial includes both daily and non-daily smokers.
- The trial is undertaken in a country with strong tobacco control measures in place, and low uptake of e-cigarettes.
- For ethical reasons, in New Zealand it was not possible to include a fourth comparison group of placebo patches.

INTRODUCTION

Smoking cessation treatments should address at least two aspects of tobacco dependence: physiological and behavioural dependence.[1] Although nicotine replacement therapies (NRT) help address the physiological dependence of cigarette smoking by providing nicotine to the body, they don't mimic the habituated tactile behaviors (involving the mouth and hands) associated with cigarette use.[2]

Electronic cigarettes (e-cigarettes) have considerable potential to help people quit smoking as they address both the physiological and behavioural dependence of tobacco smoking.[3 4] These devices deliver nicotine by a form of aerosolisation (popularly known as vaping), and are likely safer to use than smoking tobacco as users have reduced exposure to tobacco toxicants.[5-10] To date, only two randomised trials with six-month abstinence outcomes have been published on the use of e-cigarettes for smoking cessation (Table 1).[11-13]

Table 1: Summary of the design and outcomes from the two published trials of e-cigarettes for smoking cessation

	ECLAT **Caponnetto et al 2013**[11]	**ASCEND** **Bullen et al 2013**[12 13]
Population	Unmotivated to quit	Motivated to quit
Eligibility	≥10 CPD for at least 5 years, 18-70 years	≥10 CPD for last year, ≥18 years
E-cigarette brand	Categoria (First generation)	Elusion (First generation)
Sample size	300 (1:1:1)	657 (4:4:1)
Intervention	7.2mg e-cigarette (n=100)** 7.2-5.4mg e-cigarette (n=100)** 0mg e-cigarette (n=100)** No behavioural support	16mg e-cigarette (n=289)** 21mg nicotine patch (n=295) 0mg e-cigarette (n=73)** Minimal behavioural support
Intervention period	12 weeks	13 weeks (includes one week pre-quit)
Follow-up	12 months	Six months

Power	75%	80%
Continuous abstinence at six months*	7.2 mg e-cigarette: 12% 7.2-5.4 mg e-cigarette: 10% 0 mg e-cigarette: 5% p=0.39	Nicotine e-cigarette: 7.3% Nicotine patches: 4.1% RD=1.51 95% CI –2.49-5.51 Nicotine e-cigarette: 7.3% Placebo e-cigarette: 5.8% RD=3.16 95% CI –2.29-8.61
Smoking reduction	**Percentage reduction in CPD at six months** 7.2 mg e-cigarette: 17% 7.2-5.4 mg e-cigarette: 19% 0 mg e-cigarette: 15% p=0.39	**Reduced CPD by ≥ 50% at six months** Nicotine e-cigarette: 57% Nicotine patches: 41% p=0.0002 Nicotine e-cigarette: 57% Placebo e-cigarette: 45% p=0.08
Time to relapse (median)	Not reported	Nicotine e-cigarette: 35 days Nicotine patches: 14 days Placebo e-cigarette: 12 days
Adverse events	No difference in frequency of events between groups at week 12 and 52	Nicotine e-cigarette: 137 events in 107 participants over six months. 0.8 events per person month Nicotine patches: 119 events in 96 participants over six months. 0.8 events per person month Placebo e-cigarette: 36 events in 26 participants over six months. 0.9 events per person month Nicotine e-cigarette vs Nicotine patches: IRR=1.05, 95% CI: 0.82-1.34, p=0.7
Serious adverse events	None reported	None related to treatment

*Primary Outcome
**_Ad libutum_ use
RD=Risk Difference
CI=Confidence Intervals
IRR=Incidence Rate Ratio
CPD=Cigarettes Per Day

In New Zealand (NZ), nicotine is regulated as a medicine, except when delivered in tobacco smoke. Up until June 2018, it was illegal to sell an e-cigarette that contained nicotine or to make a cessation claim about e-cigarettes, because Medsafe (NZ's authority for licensing medicines) considered e-cigarettes a medicine if a cessation claim was made, or when supplied with nicotine. The case for maintaining the status quo in NZ (i.e. only nicotine-free e-cigarettes available for sale) was that the efficacy of e-cigarettes is largely due to their behavioural replacement for conventional cigarettes. Indeed, some studies report a reduction in cravings to smoke with nicotine-free e-cigarettes,[12 13] and point to some degree of support for cessation. Prior to June 2018, if an e-cigarette user in NZ wanted to have nicotine, they could combine the use of an e-cigarette with NRT. However, to date no trial has investigated the impact of combining NRT and e-cigarettes on smoking abstinence. There is good evidence that combining NRT products (e.g. slow acting nicotine patches combined with faster-acting oral products, such as lozenges, gum or mouth spray) is more effective than monotherapy alone, and as safe.[14]

In 2015 we received funding for a clinical trial to assess the effectiveness and safety of combining nicotine patches with e-cigarettes (with and without nicotine) on smoking abstinence at six months. Our primary hypothesis is that 21mg nicotine patches plus 18 mg/mL nicotine e-cigarettes will be more effective at helping smokers quit than 21mg nicotine patches plus nicotine-free e-cigarettes. Our secondary hypothesis is that combination therapy (i.e. 21mg nicotine patches plus 18 mg/mL nicotine e-cigarettes) will be more effective than monotherapy (i.e. 21mg nicotine patches alone).

METHODS AND ANALYSIS

Choice of design and intervention

A three-arm, randomised-controlled, parallel group, superiority trial is used to answer the research question. Whilst it is logical to include a fourth group (i.e. placebo patches), it is unethical in NZ to deny a smoker access to a proven smoking cessation medication. For this reason, only an active nicotine patch is used. A 21mg (24 hour) nicotine patch was selected as it is the standard patch strength used in NZ (Habitrol® 21mg patch, Novartis Consumer Health Australasia Pty). A second generation e-cigarette starter kit (eVOD brand, 1.8 OHM: Kangertech, Shenzhen GuangDong, China) was chosen, with an 18mg/mL nicotine strength. Each kit contains two batteries, two cartridges, two charging kits, one carry case, and five atomisers. Participants can choose one of two tobacco e-juice flavours, based on the type of tobacco they usually smoke (i.e. roll-your-own or factory-made: 38% of NZ smokers use roll-your-own tobacco exclusively[15]). The e-liquid (60/40 PG/VG ratio) is sourced from

Nicopharm, Australian (https://www.nicopharm.com.au/). The e-juice will be independently assessed to verify nicotine content is as labeled, and to check for contaminants. For the nicotine e-liquid, a variability of +/- 10% nicotine concentration will be considered acceptable. Batch-to-batch variability of nicotine content in the e-liquid will also be assessed.

Patient and public involvement

Smokers and members of the public were not involved in the development of the research question, study design, recruitment or trial conduct. Choice of outcome measures was not directly informed by smokers' priorities, experience, or preferences, nor has the burden of the intervention been assessed by smokers. However, the brand and type of e-cigarette, nicotine strength for the e-juice, and choice of flavours was selected based on advice received from members of the NZ vaping retailer community. A summary of the study results will be posted/emailed to all trial participants.

Study population

People who smoke cigarettes (daily and non-daily), currently live in NZ, state that they are motivated to quit within the next two weeks, and meet the eligibility criteria outlined below. Non-daily smokers are included for a number of reasons: 1) there is a drive to reach NZ's smokefree2025 goal; 2) there is limited research funding in NZ, so research efforts should endeavor to reach as many smokers as possible; 3) unpublished data from the NZ Health Survey show an increase in the number of non-daily smokers (from 7.7% in 2006/07, to 9.3% in 2012/13); and 4) these non-daily smokers are less likely to receive cessation support. The risk versus benefit analysis of including this population in the trial considered the harms of continued smoking (and high likelihood of receiving no cessation support) versus the potential risk of exposure to higher than normal nicotine levels via the trial interventions (acknowledging that users will self-titrate).

Eligibility criteria

Participants will be eligible if they are: at least 18 years of age, able to provide verbal consent, have access to a telephone, and prepared to use the trial treatments. Only one person per household is eligible. There is no language restriction for participation in the trial, as translation services are available. Women who self-report that they are pregnant or breastfeeding will be excluded from the trial, as will current users of NRT, people currently enrolled in another smoking cessation programme or cessation study, people who have used an e-cigarette for smoking cessation for more than one week anytime in the last year, or current users of non-nicotine based cessation therapies (e.g. buproprion, clonidine, nortriptyline or varenicline). People are also ineligible if they have any contraindications to

nicotine patches (i.e. they have had a heart attack, stroke or severe angina within the previous two weeks, as per recommendations by the NZ Quitline) or e-cigarette (i.e. they self-report a history of severe allergies and/or poorly controlled asthma). There are no other exclusion criteria - as a pragmatic trial all people who smoke are eligible for the trial, irrespective of their medical/psychiatric history.

Recruitment

Potential participants will be recruited via media advertising/social media and directed to contact the study centre at the University of Auckland's National Institute for Health Innovation (NIHI) by freephone, email, Facebook or through the study website.

Randomisation, allocation concealment and sequence generation

Potential participants will be phoned by a research assistant and provided with further information about the study. A two-step verbal consent process will be used, where permission will be sought from participants to 1) undertake screening, and 2) undertake randomisation. A copy of the patient information sheet and electronic consent form will be posted/emailed to participants for their records. After screening, baseline data will be collected and participants will be allocated to one of the three study groups in a 1:4:4 ratio (21mg nicotine patch alone: 21mg nicotine patch plus 18mg/mL nicotine e-cigarette: 21mg nicotine patch plus nicotine-free e-cigarette) using stratified block randomisation (block size of nine). Randomisation will be stratified by ethnicity (Māori, non-Māori) to ensure an equal balance in this key prognostic factor. The computer-generated randomisation sequence will be prepared by the study statistician.

Blinding

Participants and all research staff (except the project manager) are blinded to the nicotine content of the e-juice (the e-juice is stored in a brown bottle), until after data lock. The project manager is not involved in any data collection or interaction with trial participants. If required, the medical practitioner who reviews all adverse event reports may request that the participant's data be un-blinded. This un-blinding will be undertaken by the study statistician.

Withdrawal

- If a participant voluntarily withdraws, no further data from the point of withdrawal will be collected. Should a participant require discontinuation of study treatment, or if they elect to cease taking treatment, data collection will continue as scheduled. If a participant discontinues treatment due to a serious adverse event, the participant will be followed until the event resolves or there is a return to a clinically acceptable medical status.

Study interventions and procedures

Participants will be randomised to one of three treatment arms:

- 14 weeks of 21mg nicotine patch alone (n=201)
- 14 weeks of 21mg nicotine patch plus 18mg/mL nicotine e-cigarette (n=804)
- 14 weeks of 21mg nicotine patch plus nicotine-free e-cigarette (n=804)

At the time of randomisation participants in all three arms will receive 10-15 minutes of telephone-based withdrawal-oriented behavioural support and advice on using their allocated product. All three groups will also receive weekly withdrawal-oriented behavioural support telephone calls (10-15 minutes) for six weeks post-randomisation, delivered by trained smoking cessation advisors. Participants will have their full supply of free nicotine patches plus, if allocated, their free e-cigarette and e-juice (four 30mL bottles) couriered to them.

Pre-quit period: At the time of randomisation, all participants will be advised to start using their nicotine patch (one per day) two weeks before their designated quit-date. During this 'pre-quit' period, those participants randomised to receive an e-cigarette will also be advised to start using their device *ad libitum* in order to familiarise themselves with use of the e-cigarette.[12 13 16 17] Participants will be provided with written instructions on how to assemble and use their e-cigarette, plus provided with a web-link to: 1) a NZ vaping industry designed document entitled "A Beginners Guide to Vaping" and 2) short on-line instruction videos hosted by a NZ-based on-line vaping retailer. This retailer will also provide a helpline number for participants to call should they need additional help or advice regarding use of the e-cigarette. The videos and helpline reflects 'real world' support offered by the vaping community in NZ for naive e-cigarette users (with the exception that no face-to-face support will be offered, although participants are free to choose to visit a vape shop and/or talk with a vaper at any time during the trial if they wish).

Intervention period: All participants will be instructed to stop smoking tobacco cigarettes from their designated quit date forwards, and continue with their allocated treatment for twelve weeks irrespective of any lapses back to smoking. All participants who have not quit by the end of follow-up will be provided with further cessation support within the context of publicly available cessation services in NZ.

Baseline assessments

The following baseline data will be collected via a phone interview with all participants:

- *Demographics*: Date of birth, gender, ethnicity, self-reported height and weight, and socio-economic position (based on education);
- *Smoking history:* Frequency of smoking (daily or non-daily, and if the latter – with what frequency), age when started, number of cigarettes smoked per day (or when smoking, for non-daily smokers), years of smoking, number of previous attempts to give up in past 12 months (including the longest time they stayed quit and the method used), type of cigarettes smoked per day (e.g. roll-your-own, factory-made), pack size and how long each pack lasts (for roll-your-own tobacco users), and whether they had tried to reduce the number of cigarettes smoked in the last 12 months;
- *Level of cigarette dependence:* Measured using the Fagerström Test for Cigarette Dependence;[18 19]
- *Other smoking related information*: Self-rated chances of quitting measured on a scale from 1 to 5 where 1= unlikely and 5= highly likely; smoking and e-cigarette use in the household; exposure to others who use e-cigarettes; smokefree home and car policies.
- *General health*: Self-reported shortness of breath, cough, asthma, Chronic Obstructive Pulmonary Disease (COPD), and current or history of mental health problems;
- *The physical signs and symptoms associated with withdrawal*: Measured using the Mood and Physical Symptoms Scale (MPSS),[20] including urge to smoke;
- *Concomitant medication*: Information about types of medication currently used.

Primary outcomes

The primary outcome will be continuous abstinence to six months post quit-date, defined according to the Russell Standard (i.e. self-report of smoking not more than five cigarettes from the quit date, supported by biochemical validation via exhaled carbon monoxide [CO] measurement).[21] CO measurements will only be undertaken at the six and 12 month time point, and will be undertaken face-to-face by a researcher or community-based cessation provider at a site convenient to the participant. A CO Monitor (Bedfont Smokerlyzer; Bedfont Scientific Ltd, Station Road, Harrietsham, Maidstone, Kent, ME17 1JA, England) will be used, with a reading of 9 ppm signifying abstinence.[21]

Secondary outcomes

Secondary outcomes will be assessed via phone interview with participants on their designated quit date, and at one, three, six and 12 months post quit-date (Table 2).

- *Continuous abstinence (1, 3 and 12 months)*: The proportion of participants that have stopped smoking, defined as self-report of smoking not more than five cigarettes from the quit date;
- *7-day point prevalence (all time points):* The proportion of participants that have stopped smoking, defined as self-report of having smoked no cigarettes (not even a puff) in the past seven days;
- *Change from baseline in the number of cigarettes smoked per day, or when smoking for non-daily smokers (all time points):* If the participant is still smoking;
- *Proportion of participants who have significantly reduced smoking (all time points):* Percentage reduction, and the proportion who have reduced the number of cigarettes smoked per day (or when smoking for non-daily smokers) by at least 50% (in order to allow comparison with the ASCEND trial[12 13]).
- *Time to first relapse from quit date:* Defined as return to daily smoking (for daily smokers);
- *Use of any other smoking cessation methods (all time points);*
- *Medication compliance (quit day, 1 and 3 months):* Participants will be asked whether they used their allocated product(s), and if not, why not. Participants who did use their allocated products(s) will be asked when they last used them, and how many days in the last week. Those allocated e-cigarettes will be asked how many mls of juice they use on a typical day (the EVod holds 2.2 mls).
- *Crossover (all time points):* Participants in the patch-only group will be asked whether they accessed and used an e-cigarette (with or without nicotine) during the trial, and if so, at what time during the trial;
- *Weight (3, 6 and 12 months):* Self-reported;
- *Change from baseline in the physical signs and symptoms associated with withdrawal (all time points)***:** Measured using the MPSS,[20] including urge to smoke;
- *Dual use (all time points):* Defined as daily use of both their allocated e-cigarette and usual cigarettes;
- *General vaping questions (all time points):* Urge to vape, whether they changed devices and/or e-juice; whether they accessed any support for using their e-cigarette (and if so, where and how useful the support was); whether anyone they see at least once a week currently uses an e-cigarette (including whether this is someone they live with or not);
- *Continuation of use (6 and 12 months):* Continued use of their allocated treatment after the end of the treatment period;
- *General health (all time points)*: Self-reported shortness of breath, cough, asthma, COPD, and mental health problems;

Table 2: Details of follow-up

	Call 1			Call 2	Call 3	Call 4	Call 5	Call 6
Timing	**Week 0**			**Quit date (QD)**	**One month after QD**	**Three months after QD**	**Six months After QD**	**12 months After QD**
Description	**Screening (S), Baseline (B), Randomisation (R)**			**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**
General data								
Eligibility criteria	X							
Consent	X							
Age and gender		X						
Height		X						
Weight		X				X	X	X
Ethnicity		X						
Education		X						
Current medication		X		X	X	X	X	X
General health		X		X	X	X	X	X
Pregnancy	X			X	X	X		
Smoking information								
Level of nicotine dependence		X						
Type of tobacco smoked		X						
Pouch size and how long lasts^		X						
Cigarettes smoked per day		X		X	X	X	X	X
Age started		X						
Years smoked		X						
Household smoking		X						
Around others that use e-cigarettes		X				X		
Previous quit attempts & method		X						
Belief in ability to quit		X		X	X			
Any smoking in last seven days				X	X	X	X	X
Any smoking since QD					X	X	X	X
Biochemical verification in those who self-report quitting							X	X
Withdrawal/urge to smoke		X		X	X	X	X	X
Follow-up details								
Quit date			X	X				
Contact details			X	X	X	X	X	X
Treatment allocation and details			X					
Use of non-NRT cessation methods								
Type of cessation method used					X	X	X	X
Intervention period								
Acceptability / perceptions					X	X	X	X
Recommendations					X	X	X	X
Medication compliance				X	X	X		
Other outcomes								
Crossover				X	X	X	X	X
Additional e-cigarette support*				X	X	X	X	X
Dual use				X	X	X	X	X
Cost				X	X	X	X	X
Continuation of allocated treatment							X	X
Side effects/serious adverse events				X	X	X	X	X
Identity*						X	X	X

^ *In people who smoke roll-your-own tobacco* QD *Quit Date* * *In those allocated e-cigarettes*

- *Belief in ability to quit and stay quit (quit date and 1 month):* measured on a scale from 1 to 5 where 1=unlikely and 5=highly likely;
- *Identity (3 and 6 months)*: Whether those allocated e-cigarettes consider themselves a smoker, a smoker still trying to quit, an ex-smoker, an ex-vapor, a vapor trying to quit smoking, a vapor trying to quit vaping, a vapor, other, or none of the above.
- *Perception of their product (1, 3, 6 and 12 months):* Participants' views on use of their allocated treatment as a smoking cessation aid;
- *Recommendations for use (1, 3, 6 and 12 months):* Whether they would recommend their allocated treatment to another smoker who wanted to quit;
- *Occurrence of specific side effects from product use (all time points);* Cough, nausea, dry mouth / throat, redness / swelling at patch site, dizziness, headache, vivid dreams, difficulty sleeping, dry skin, itchiness, other.
- *Serious adverse events (all time points*); Serious adverse events will be recorded and described as per International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, and followed to resolution or stabilisation.
- *Concomitant medication (all time points)*;
- *Cost information:* Cost-per-quitter, cost-per-person reducing their daily cigarette consumption (or when smoking for non-daily smokers) and the incremental cost effectiveness ratio, if the intervention is indeed shown to be more effective than the comparison condition. The tobacco expenditure savings to individual smokers will also be calculated using data on the amount smoked prior to quitting and the price of the particular products smoked.

Sample size

To detect an absolute difference of 8% in six-month continuous abstinence rates between the 21mg nicotine patch + nicotine e-cigarette group and the 21mg nicotine patch + nicotine-free e-cigarette group, 804 participants are needed in each group for 90% power (and 600 for 80% power). To detect an absolute difference of 15% in six month continuous abstinence rates between the 21mg nicotine patch group and the 21mg nicotine patch + nicotine e-cigarette group, 201 participants are needed in each group for 90% power (and 150 for 80% power). A total sample size of 1,809 (804 in both e-cigarette groups and 201 in the nicotine patch group) is needed for 90% power, with p=0.05 and adjusted for 20% loss to follow-up[12] (Figure 1).

<insert Figure 1 here>

A six month quit rate of 16% was assumed for the nicotine patch group, based on the average quit rate observed in the Cochrane review for nicotine patches vs placebo/no NRT control.[14] We estimated a six month quit rate of 31% for the nicotine patch + nicotine e-cigarette group based on the quit rate observed in a trial (n=239) comparing 'nicotine patches plus nicotine spray' against 'nicotine patches plus placebo spray'.[22] A six month quit rate of 23% for the nicotine patch + nicotine-free e-cigarette group was assumed, based on a pragmatic trial (n=1410) undertaken in NZ comparing use of NRT combined with very low nicotine cigarettes.[23] Our previous experience of recruiting smokers from the community suggests recruitment will take 18 months.[12]

Data management

Members of the trial steering committee will provide trial oversight, with day-to-day management of the trial undertaken by the project manager, project coordinator, and data manager. Study data will be collected by research assistants and directly entered into an electronic data management system (REDCap).[24] All data will be securely stored, regularly backed-up, and retained for 10 years from data-lock. The study will be independently monitored after ten participants have been randomised, at study close-out, and twice during the trial. According to the guidelines proposed by Ellenburg et al. (2002) a Data Safety and Monitoring Committee is not required.[25]

Statistical analysis

Analyses will be performed using SAS (9.4) and R.[26] No interim analyses are planned. Analysis will be carried out on an intention-to-treat basis (i.e. all participants as originally allocated after randomisation will be analysed, and all participants lost to follow-up will be assumed to be smoking), with the quit rates, relative risks (RR), absolute risks and 95% CI calculated for the primary and secondary comparison. Treatment groups will be compared using χ^2 tests, with multiple logistic regression analysis adjusting for other variables as appropriate. Sensitivity analyses will be undertaken to determine the impact of using varying cut-offs for CO measurements (given lack of consensus about the best reading to use), and secondary analyses performed to correct overall cessation rates for discordance between reported and verified cessation. Sensitivity analyses will also be carried out to determine the effect of missing data. If the level of missing data is >20%, multiple imputation will be employed.[27] A per-protocol analysis will also be performed for the primary outcome where only those participants who completed the treatment originally allocated will be included (i.e. participants with major protocol violations, such as cross-overs treatments, withdrawals, and loss to follow-up will be excluded). The consistency of effects for pre-specified subgroups will

be assessed using tests for heterogeneity. Subgroups will be based on age, sex, ethnicity, education, level of nicotine dependence, smoking frequency at baseline (daily/non-daily), and self-efficacy of quitting. Data related to smoking reduction will be reported separately for daily and non-daily smokers. A repeated measures model will be used to analyse change from baseline in cigarettes smoked per day (in non-abstainers), and will adjust for baseline value. Kaplan-Meier curves, the log rank test, and Cox proportional hazards regression analysis will be used to analyse time-to-relapse. Serious adverse events will be defined according to the ICH-GCP E6 guidelines, categorised by the study doctor (masked to intervention product) as definitely, probably, possibly, unlikely, or not related to the intervention, and coded by a medical coder (masked to intervention product) according to ICD-10 AM (8th edition). Events will be analysed by treatment group and association with study treatment. If the primary outcome of the trial is positive analyses will be undertaken to model the marginal cost-per-quitter, taking a health sector perspective. The tobacco expenditure savings to individual smokers will also be calculated (for those who quit and cut down) to give a more societal perspective on the financial benefits (especially to low-income smokers). For those participants who cut down their tobacco consumption by ≥50%, the cost-per-person reducing their daily cigarette consumption will be calculated.

ETHICS AND DISSEMINATION

Ethics approval was obtained on the 16/09/2015 from the Northern A Health and Disability Ethics Committee (15/NTA/123). Participants are fully informed of their rights to withdraw, the risk/benefits of participating, the confidentiality of their data, and that they may be eligible for compensation from the NZ Accident Compensation Corporation or private health/life insurance should they experience any injury as a result of participating in the trial. Approval from the Standing Committee on Therapeutic Trials was obtained on the 28/09/2015 for use of nicotine e-cigarettes. This study is registered with ClinicalTrials.gov (NCT02521662). The trial dataset will be available from the corresponding author for use in any meta-analyses, on reasonable request. The dissemination plan includes national/international media coverage, publication in a high-impact peer-reviewed journal, and oral presentations to relevant national/international audiences.

DISCUSSION

The ASCEND-II trial is pragmatic in design and investigates the effectiveness of the trial interventions, enabling the findings to be more readily generalised to the unique tobacco control environment of NZ, than would be the case in an efficacy trial. Tobacco control measures have been implemented in NZ for the past 30 years. As a result tobacco is

expensive (NZ$25.30, US$18.20, €15.44 as 24/08/17 for a pack of 20 cigarettes), tobacco advertising is banned, point of sale display bans are in effect, and cessation support and medication (including combination NRT) is accessible and heavily subsidised. Despite these measures, in 2015 16% of the NZ adult population (≥15 years) were current smokers (14% daily), including 39% of Māori[28] (indigenous NZers who comprise 15% of the population[29]) and 25% of Pacific people[28] (who comprise 5% of the population[29]). Within this environment, e-cigarette usage in NZ is increasing. In 2011/12, a survey of 480 adults (≥ 18 years, smokers and recent quitters) found that 7% had ever purchased e-cigarettes.[30] In 2016, a survey of 3,854 NZ adults (>15 years old, smokers and non-smokers) reported 17% had tried an e-cigarette and 2% were current users (defined as used at least daily, weekly or monthly).[31]

The pragmatic nature of the trial is highlighted by our use of a PRECIS-2 (PRagmatic-Explanatory Continuum Indicator Summary-2) wheel.[32] The wheel has nine spokes (or domains) that focus on each aspect of the trial, namely: eligibility, recruitment, setting, organisation, flexibility (delivery of the intervention), flexibility (adherence to the intervention), follow-up, primary outcome, and primary analysis. Each domain is scored on a 5-point Likert scale ranging from 1 “very explanatory” to 5 “very pragmatic”. More pragmatic trials have a larger wheel, whilst more explanatory trials have a smaller wheel. The tool also allows the reader to see that certain aspects of a trial may vary along the pragmatic-explanatory continuum. Five authors (NW, MV, TK, VP, CB) independently assessed the design according to the nine domains and the average scores for each domain are indicated on each spoke in Figure 2 (with the range in brackets).

<Insert Figure 2 here>

Current status

Recruitment started on 16th March 2016, with final data collection expected to be completed July 2018. This paper reports on protocol version 4.0, 10th February 2017. The protocol was amended in April 2017, driven by the need to shorten the interview time, reduce participant burden and ensure the trial can finish on budget and on time. The amendments involved removal of the 12-month assessment and several secondary outcomes, namely: smokefree cars/homes (baseline); belief in ability to quit for good (one month); MPSS and urge to smoke (all time-points); general vaping questions (all time-points); general health questions (quit date, one month); perceptions of their allocated product; and recommendations for use (one and six months). Details on the subset of participants that provided data on these removed secondary outcomes will be published. In June 2018 (four years after the ASCEND-

II trial was designed and funded), the NZ Ministry of Health legalised the sale and supply of nicotine e-cigarettes as consumer products.

AUTHORS' CONTRIBUTIONS

Authorship follows the ICMJE guidelines. NW, VP, GL, ML and CB conceived the original idea for the trial, sought and obtained funding for the trial, and wrote the study protocol. TK is the project manager responsible for the day-to-day running of the trial, whilst MV is the research fellow involved in the trial. VP will undertake all data analyses. This protocol paper was written by MV and NW with input from all co-authors. NW is guarantor for this paper. All authors read and approved the final manuscript.

FUNDING STATEMENT

This trial is funded by a three year project grant from the Health Research Council of NZ (15/202). Approximately NZ$600,000 (€350,000 or US$400,000) was available to run the trial. The e-cigarettes for this trial are being purchased directly from a New Zealand e-cigarette retailer - NZVAPOR. NZVAPOR are not involved in the design, conduct or analysis of the trial, but are providing on-line and phone support to participants regarding use of their allocated e-cigarettes. The e-cigarettes to be used in the trial and NZVAPOR (including the Managing Director) have no links with the tobacco industry. The e-juice for the trial is purchased directly from Nicopharm, Australia. The nicotine patches are supplied by the NZ Government via their contract with Novartis. Nicopharm and Novartis are not involved in the design, conduct or analysis of the trial and have no known links with the tobacco industry. Independent testing of the nicotine content of the e-juice will be undertaken by the NicoTar group at Roswell Park Cancer Institute, Buffalo, New York, USA.

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COMPETING INTERESTS STATEMENT

No authors have received financial support for the submitted work from any companies with a financial interest in the products under investigation. CB has previously undertaken research funded by NicoNovum prior to its sale to RJ Reynolds. CB has received benefits in kind (accommodation expenses) from a manufacturer of smoking cessation medications. NW has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support

from a manufacturer of smoking cessation medications (but over five year ago). NW, CB, MV, GL and VP are currently involved in a clinical trial in which varenicline and matching placebo are supplied by Pfizer under their Investigator-Initiated Research Program. MV has previously undertaken research supported by an unrestricted grant from Pfizer. None of the authors' spouses, partners, or children have financial relationships that may be relevant to the submitted work. All authors have no non-financial interests that may be relevant to the submitted work

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Figure 1: Estimated effect sizes for planned comparisons

Figure 2. Design of the trial along the 'pragmatic to explanatory' continuum

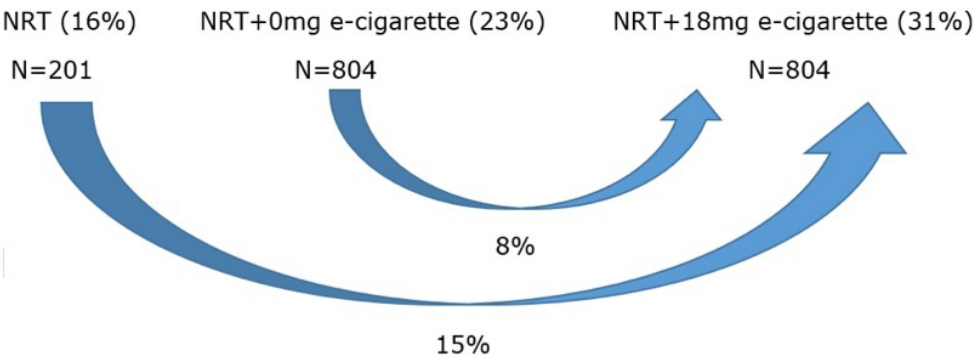

Figure 1: Estimated effect sizes for planned comparisons

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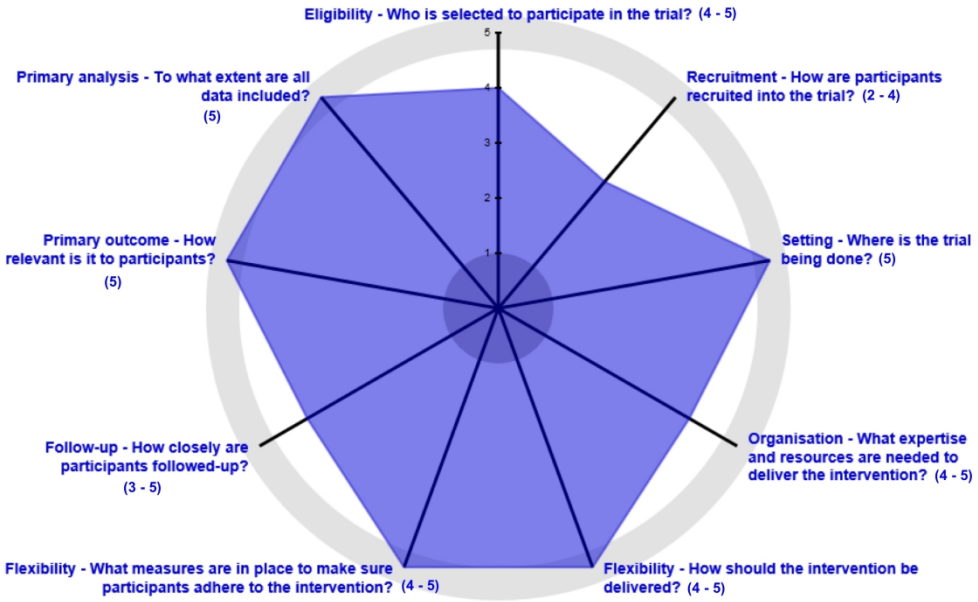

Figure 2. Design of the trial along the 'pragmatic to explanatory' continuum

297x209mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Pg	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
Protocol version	16	Date and version identifier
Funding	18	Sources and types of financial, material, and other support
Roles and responsibilities	1,18	Names, affiliations, and roles of protocol contributors
	N/A	Name and contact information for the trial sponsor
	18	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	14	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	4-6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6-7	Explanation for choice of comparators
Objectives	6	Specific objectives or hypotheses
Trial design	6	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	2,7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	2,7-8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	2,9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	8	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	N/A	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	10-13	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	9-13	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	12	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	13-14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	8	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	8	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	8	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	8	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	8	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	8	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	9-13	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	8	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	14	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	14-15	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	14-15	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	14-15	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring		
Data monitoring	14	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	N/A	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	13,15	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	14	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	15	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	16	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	8	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	N/A	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	15	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	18	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	15	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy	15	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	18	Authorship eligibility guidelines and any intended use of professional writers
	15	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	-	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	N/A	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6, 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	16-17
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	16-17
Sample size	7a	How sample size was determined	13-14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	14-15
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14-15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n.a.
	13b	For each group, losses and exclusions after randomisation, together with reasons	n.a.
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n.a.
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n.a.
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n.a.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n.a.
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n.a.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n.a.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n.a.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n.a.
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n.a.
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n.a.
Other information			
Registration	23	Registration number and name of trial registry	2, 15
Protocol	24	Where the full trial protocol can be accessed, if available	n.a.
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023659.R2
Article Type:	Protocol
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Complete List of Authors:	Walker, N; University of Auckland, National Institute for Health Innovation Verbiest, Marjolein; University of Auckland, National Institute for Health Innovation Kurdziel, Tomasz; University of Auckland, National Institute for Health Innovation Laking, George; University of Auckland, Department of Oncology Laugesen, Murray; Health New Zealand Ltd Parag, Varsha; University of Auckland, National Institute for Health Innovation Bullen , Chris ; University of Auckland, National Institute for Health Innovation
Primary Subject Heading:	Public health
Secondary Subject Heading:	Smoking and tobacco, Addiction, Research methods
Keywords:	e-cigarettes, nicotine patch, Clinical trial, smoking cessation, effectiveness, safety

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.

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Running head: E-cigarettes and patches for smoking cessation

Word count (abstract): 299

Word count (paper): 4000

Keywords: Electronic cigarettes, E-cigarettes, Cessation, Nicotine Patch, Effectiveness, Safety, Randomised controlled trial.

ABSTRACT

Introduction: Evidence indicates e-cigarettes can help people quit smoking, however more confirmatory trials are needed. To date, no trials have evaluated the effectiveness and safety of combining nicotine patches with e-cigarettes (with and without nicotine) for smoking cessation.

Methods and analysis: This study is a pragmatic, three-arm, community-based, single-blind, randomised trial undertaken in New Zealand. Eligible participants are daily/non-daily smokers, aged ≥18 years, naive e-cigarette users, and motivated to quit smoking in the next two weeks. Participants (n=1809) recruited using multi-media advertising, are randomised to 14 weeks of: 1) 21mg nicotine patches (n=201); 2) 21mg nicotine patches + 18mg/mL nicotine e-cigarette (n=804); or 3) 21mg nicotine patches + nicotine-free e-cigarette (n=804). Participants receive weekly withdrawal-oriented behavioural support calls for six weeks post-randomisation.

The primary outcome is self-reported biochemically verified continuous abstinence (CA) at six months post quit-date. The primary comparison is nicotine patch + nicotine-free e-cigarette versus nicotine patch + nicotine e-cigarette, and the secondary comparison is nicotine patch versus nicotine patch + nicotine e-cigarette (90% power, p=0.05, to detect an absolute difference in six-month CA rates of 8% and 15% respectively). Secondary outcomes, collected by phone interview at quit date, then one, three, six and 12 months post-quit date, include: self-reported CA, 7-day point prevalence abstinence, cigarettes per day (if smoking, or when smoking for non-daily smokers), time to relapse (if returned to smoking), belief in ability to quit, use of other cessation support, side effects/serious adverse events, treatment compliance, seeking additional support around e-cigarette use, daily use of both e-cigarettes and cigarettes, use of treatment past 14 weeks, views on treatment and recommendation to others, weight, and cost-per-quitter.

Ethics and dissemination: The Northern A Health and Disability Ethics Committee approved the trial. Findings will be disseminated through publication, conference/meeting presentations, and media.

Trial registration number: ClinicalTrials.gov (NCT02521662)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first trial to investigate the effectiveness and safety of combining nicotine patches and e-cigarettes on smoking abstinence.
- This is the first large community-based trial testing a second generation e-cigarette for smoking cessation, with choice of device and juice undertaken in consultation with members of the vaping industry.
- The trial is undertaken in a country with strong tobacco control measures in place, and low uptake of e-cigarettes.
- The trial is pragmatic in design, with open eligibility and no participant payments, enabling greater generalisability.
- For ethical reasons, in New Zealand it was not possible to include a fourth comparison group of placebo patches.

INTRODUCTION

Smoking cessation treatments should address at least two aspects of tobacco dependence: physiological and behavioural dependence.[1] Although nicotine replacement therapies (NRT) help address the physiological dependence of cigarette smoking by providing nicotine to the body, they don't mimic the habituated tactile behaviors (involving the mouth and hands) associated with cigarette use.[2]

Electronic cigarettes (e-cigarettes) have considerable potential to help people quit smoking as they address both the physiological and behavioural dependence of tobacco smoking.[3 4] These devices deliver nicotine by a form of aerosolisation (popularly known as vaping), and are likely safer to use than smoking tobacco as users have reduced exposure to tobacco toxicants.[5-10] To date, only two randomised trials with six-month abstinence outcomes have been published on the use of e-cigarettes for smoking cessation (Table 1).[11-13]

Table 1: Summary of the design and outcomes from the two published trials of e-cigarettes for smoking cessation

	ECLAT **Caponnetto et al 2013**[11]	**ASCEND** **Bullen et al 2013**[12 13]
Population	Unmotivated to quit	Motivated to quit
Eligibility	≥10 CPD for at least 5 years, 18-70 years	≥10 CPD for last year, ≥18 years
E-cigarette brand	Categoria (First generation)	Elusion (First generation)
Sample size	300 (1:1:1)	657 (4:4:1)
Intervention	7.2mg e-cigarette (n=100)** 7.2-5.4mg e-cigarette (n=100)** 0mg e-cigarette (n=100)** No behavioural support	16mg e-cigarette (n=289)** 21mg nicotine patch (n=295) 0mg e-cigarette (n=73)** Minimal behavioural support
Intervention period	12 weeks	13 weeks (includes one week pre-quit)

Follow-up	12 months	Six months
Power	75%	80%
Continuous abstinence at six months*	7.2 mg e-cigarette: 12% 7.2-5.4 mg e-cigarette: 10% 0 mg e-cigarette: 5% p=0.39	Nicotine e-cigarette: 7.3% Nicotine patches: 4.1% RD=1.51 95% CI −2.49-5.51 Nicotine e-cigarette: 7.3% Placebo e-cigarette: 5.8% RD=3.16 95% CI −2.29-8.61
Smoking reduction	**Percentage reduction in CPD at six months** 7.2 mg e-cigarette: 17% 7.2-5.4 mg e-cigarette: 19% 0 mg e-cigarette: 15% p=0.39	**Reduced CPD by ≥ 50% at six months** Nicotine e-cigarette: 57% Nicotine patches: 41% p=0.0002 Nicotine e-cigarette: 57% Placebo e-cigarette: 45% p=0.08
Time to relapse (median)	Not reported	Nicotine e-cigarette: 35 days Nicotine patches: 14 days Placebo e-cigarette: 12 days
Adverse events	No difference in frequency of events between groups at week 12 and 52	Nicotine e-cigarette: 137 events in 107 participants over six months. 0.8 events per person month Nicotine patches: 119 events in 96 participants over six months. 0.8 events per person month Placebo e-cigarette: 36 events in 26 participants over six months. 0.9 events per person month Nicotine e-cigarette vs Nicotine patches: IRR=1.05, 95% CI: 0.82-1.34, p=0.7

Serious adverse events	None reported	None related to treatment

*Primary Outcome
RD=Risk Difference
IRR=Incidence Rate Ratio

***Ad libutum* use
CI=Confidence Intervals
CPD=Cigarettes Per Day

In New Zealand (NZ), nicotine is regulated as a medicine, except when delivered in tobacco smoke. Up until June 2018, it was illegal to sell an e-cigarette that contained nicotine or to make a cessation claim about e-cigarettes, because Medsafe (NZ's authority for licensing medicines) considered e-cigarettes a medicine if a cessation claim was made, or when supplied with nicotine. The case for maintaining the status quo in NZ (i.e. only nicotine-free e-cigarettes available for sale) was that the efficacy of e-cigarettes is largely due to their behavioural replacement for conventional cigarettes. Indeed, some studies report a reduction in cravings to smoke with nicotine-free e-cigarettes,[12 13] and point to some degree of support for cessation. Prior to June 2018, if an e-cigarette user in NZ wanted to have nicotine, they could combine the use of an e-cigarette with NRT. However, to date no trial has investigated the impact of combining NRT and e-cigarettes on smoking abstinence. There is good evidence that combining NRT products (e.g. slow acting nicotine patches combined with faster-acting oral products, such as lozenges, gum or mouth spray) is more effective than monotherapy alone, and as safe.[14]

In 2015 we received funding for a clinical trial to assess the effectiveness and safety of combining nicotine patches with e-cigarettes (with and without nicotine) on smoking abstinence at six months. Our primary hypothesis is that 21mg nicotine patches plus 18 mg/mL nicotine e-cigarettes will be more effective at helping smokers quit than 21mg nicotine patches plus nicotine-free e-cigarettes. Our secondary hypothesis is that combination therapy (i.e. 21mg nicotine patches plus 18 mg/mL nicotine e-cigarettes) will be more effective than monotherapy (i.e. 21mg nicotine patches alone).

METHODS AND ANALYSIS

Choice of design and intervention

A three-arm, randomised-controlled, parallel group, superiority trial is used to answer the research question. Whilst it is logical to include a fourth group (i.e. placebo patches), it is unethical in NZ to deny a smoker access to a proven smoking cessation medication. For this reason, only an active nicotine patch is used. A 21mg (24 hour) nicotine patch was selected as it is the standard patch

strength used in NZ (Habitrol® 21mg patch, Novartis Consumer Health Australasia Pty). A second generation e-cigarette starter kit (eVOD brand, 1.8 OHM: Kangertech, Shenzhen GuangDong, China) was chosen, with an 18mg/mL nicotine strength. Each kit contains two batteries, two cartridges, two charging kits, one carry case, and five atomisers. Participants can choose one of two tobacco e-juice flavours, based on the type of tobacco they usually smoke (i.e. roll-your-own or factory-made: 38% of NZ smokers use roll-your-own tobacco exclusively[15]). The e-liquid (60/40 PG/VG ratio) is sourced from Nicopharm, Australian (https://www.nicopharm.com.au/). The e-juice will be independently assessed to verify nicotine content is as labeled, and to check for contaminants. For the nicotine e-liquid, a variability of +/- 10% nicotine concentration will be considered acceptable. Batch-to-batch variability of nicotine content in the e-liquid will also be assessed.

Patient and public involvement

Smokers and members of the public were not involved in the development of the research question, study design, recruitment or trial conduct. Choice of outcome measures was not directly informed by smokers' priorities, experience, or preferences, nor has the burden of the intervention been assessed by smokers. However, the brand and type of e-cigarette, nicotine strength for the e-juice, and choice of flavours was selected based on advice received from members of the NZ vaping retailer community. A summary of the study results will be posted/emailed to all trial participants.

Study population

People who smoke cigarettes (daily and non-daily), currently live in NZ, state that they are motivated to set a quit date within the next two weeks, and meet the eligibility criteria outlined below. Non-daily smokers are included for a number of reasons: 1) there is a drive to reach NZ's smokefree2025 goal; 2) there is limited research funding in NZ, so research efforts should endeavor to reach as many smokers as possible; 3) unpublished data from the NZ Health Survey show an increase in the number of non-daily smokers (from 7.7% in 2006/07, to 9.3% in 2012/13); and 4) these non-daily smokers are less likely to receive cessation support. The risk versus benefit analysis of including this population in the trial considered the harms of continued smoking (and high likelihood of receiving no cessation support) versus the potential risk of exposure to higher than normal nicotine levels via the trial interventions (acknowledging that users will self-titrate).

Eligibility criteria

Participants will be eligible if they are: at least 18 years of age, able to provide verbal consent, have access to a telephone, and prepared to use the trial treatments. Only one person per household is eligible. There is no language restriction for participation in the trial, as translation services are available. Women who self-report that they are pregnant or breastfeeding will be excluded from the trial, as will current users of NRT, people currently enrolled in another smoking cessation programme or cessation study, people who have used an e-cigarette for smoking cessation for more than one week anytime in the last year, or current users of non-nicotine based cessation therapies (e.g. bupropion, clonidine, nortriptyline or varenicline). People are also ineligible if they have any contraindications to nicotine patches (i.e. they have had a heart attack, stroke or severe angina within the previous two weeks, as per recommendations by the NZ Quitline) or e-cigarette (i.e. they self-report a history of severe allergies and/or poorly controlled asthma). There are no other exclusion criteria - as a pragmatic trial all people who smoke are eligible for the trial, irrespective of their medical/psychiatric history.

Recruitment

Potential participants will be recruited via media advertising/social media and directed to contact the study centre at the University of Auckland's National Institute for Health Innovation (NIHI) by freephone, email, Facebook or through the study website.

Randomisation, allocation concealment and sequence generation

Potential participants will be phoned by a research assistant and provided with further information about the study. A two-step verbal consent process will be used (undertaken within the one call), where permission will be sought from participants to 1) undertake screening, and 2) undertake randomisation. A copy of the patient information sheet and electronic consent form will be posted/emailed to participants for their records. After screening, baseline data will be collected and participants will be allocated to one of the three study groups in a 1:4:4 ratio (21mg nicotine patch alone: 21mg nicotine patch plus 18mg/mL nicotine e-cigarette: 21mg nicotine patch plus nicotine-free e-cigarette) using stratified block randomisation (block size of nine). Randomisation will be stratified by ethnicity (Māori, non-Māori) to ensure an equal balance in this key prognostic factor. The computer-generated randomisation sequence will be prepared by the study statistician.

Blinding

Participants and all research staff (except the project manager) are blinded to the nicotine content of the e-juice (the e-juice is stored in a brown bottle), until after data lock. The project manager is

not involved in any data collection or interaction with trial participants. If required, the medical practitioner who reviews all adverse event reports may request that the participant's data be un-blinded. This un-blinding will be undertaken by the study statistician.

Withdrawal

- If a participant voluntarily withdraws, no further data from the point of withdrawal will be collected. Should a participant require discontinuation of study treatment, or if they elect to cease taking treatment, data collection will continue as scheduled. If a participant discontinues treatment due to a serious adverse event, the participant will be followed until the event resolves or there is a return to a clinically acceptable medical status.

Study interventions and procedures

Participants will be randomised to one of three treatment arms:

- 21mg nicotine patch alone (n=201)
- 21mg nicotine patch plus 18mg/mL nicotine e-cigarette (n=804)
- 21mg nicotine patch plus nicotine-free e-cigarette (n=804)

Participants will receive 14 weeks of treatment, consisting of a two week pre-quit period to familiarise themselves with their allocated product(s) and 12 weeks post-quit treatment.[12 13 16 17] At the time of randomisation participants in all three arms will receive 10-15 minutes of telephone-based withdrawal-oriented behavioural support (based on cognitive behavioural therapy) and advice on using their allocated product. All three groups will also receive weekly withdrawal-oriented behavioural support telephone calls (10-15 minutes) for six weeks post-randomisation, delivered by trained smoking cessation advisors. Participants will have their full supply of free nicotine patches plus, if allocated, their free e-cigarette and e-juice (four 30mL bottles) couriered to them.

Pre-quit period: At the time of randomisation, all participants will be advised to start using their nicotine patch (one per day) two weeks before their designated quit-date. During this 'pre-quit' period, those participants randomised to receive an e-cigarette will also be advised to start using their device *ad libitum* in order to familiarise themselves with use of the e-cigarette.[12 13 16 17] Participants will be provided with written instructions on how to assemble and use their e-cigarette, plus provided with a web-link to: 1) a NZ vaping industry designed document entitled "A Beginners Guide to Vaping" and 2) short on-line instruction videos hosted by a NZ-based on-line vaping

retailer. This retailer will also provide a helpline number for participants to call should they need additional help or advice regarding use of the e-cigarette. The videos and helpline reflects 'real world' support offered by the vaping community in NZ for naive e-cigarette users (with the exception that no face-to-face support will be offered, although participants are free to choose to visit a vape shop and/or talk with a vaper at any time during the trial if they wish).

Intervention period: All participants will be instructed to stop smoking tobacco cigarettes from their designated quit date forwards, and continue with their allocated treatment for twelve weeks irrespective of any lapses back to smoking. All participants who have not quit by the end of follow-up will be provided with further cessation support within the context of publicly available cessation services in NZ.

Baseline assessments

The following baseline data will be collected via a phone interview with all participants:

- *Demographics*: Date of birth, gender, ethnicity, self-reported height and weight, and socio-economic position (based on education);
- *Smoking history:* Frequency of smoking (daily or non-daily, and if the latter – with what frequency), age when started, number of cigarettes smoked per day (or when smoking, for non-daily smokers), years of smoking, number of previous attempts to give up in past 12 months (including the longest time they stayed quit and the method used), type of cigarettes smoked per day (e.g. roll-your-own, factory-made), pack size and how long each pack lasts (for roll-your-own tobacco users), and whether they had tried to reduce the number of cigarettes smoked in the last 12 months;
- *Level of cigarette dependence:* Measured using the Fagerström Test for Cigarette Dependence;[18 19]
- *Other smoking related information*: Self-rated chances of quitting measured on a scale from 1 to 5 where 1=unlikely and 5=highly likely; smoking and e-cigarette use in the household; exposure to others who use e-cigarettes; smokefree home and car policies.
- *General health*: Self-reported shortness of breath, cough, asthma, Chronic Obstructive Pulmonary Disease (COPD), and current or history of mental health problems;
- *The physical signs and symptoms associated with withdrawal*: Measured using the Mood and Physical Symptoms Scale (MPSS),[20] including urge to smoke;
- *Concomitant medication*: Information about types of medication currently used.

Primary outcomes

The primary outcome will be continuous abstinence to six months post quit-date, defined according to the Russell Standard (i.e. self-report of smoking not more than five cigarettes from the quit date, supported by biochemical validation via exhaled carbon monoxide [CO] measurement).[21] CO measurements will only be undertaken at the six and 12 month time point, and will be undertaken face-to-face by a researcher or community-based cessation provider at a site convenient to the participant. A CO Monitor (Bedfont Smokerlyzer; Bedfont Scientific Ltd, Station Road, Harrietsham, Maidstone, Kent, ME17 1JA, England) will be used, with a reading of 9 ppm signifying abstinence.[21]

Secondary outcomes

Secondary outcomes will be assessed via phone interview with participants on their designated quit date, and at one, three, six and 12 months post quit-date (Table 2).

- *Continuous abstinence (1, 3 and 12 months)*: The proportion of participants that have stopped smoking, defined as self-report of smoking not more than five cigarettes from the quit date;
- *7-day point prevalence (all time points):* The proportion of participants that have stopped smoking, defined as self-report of having smoked no cigarettes (not even a puff) in the past seven days;
- *Change from baseline in the number of cigarettes smoked per day, or when smoking for non-daily smokers (all time points):* If the participant is still smoking;
- *Proportion of participants who have significantly reduced smoking (all time points):* Percentage reduction, and the proportion who have reduced the number of cigarettes smoked per day (or when smoking for non-daily smokers) by at least 50% (in order to allow comparison with the ASCEND trial[12 13]).
- *Time to first relapse from quit date:* Defined as return to daily smoking (for daily smokers);
- *Use of any other smoking cessation methods (all time points);*
- *Medication compliance (quit day, 1 and 3 months):* Participants will be asked whether they used their allocated product(s), and if not, why not. Participants who did use their allocated products(s) will be asked when they last used them, and how many days in the last week. Those allocated e-cigarettes will be asked how many mls of juice they use on a typical day (the EVod holds 2.2 mls).

- *Crossover (all time points):* Participants in the patch-only group will be asked whether they accessed and used an e-cigarette (with or without nicotine) during the trial, and if so, at what time during the trial;
- *Weight (3, 6 and 12 months):* Self-reported;
- *Change from baseline in the physical signs and symptoms associated with withdrawal (all time points):* Measured using the MPSS,[20] including urge to smoke;
- *Dual use (all time points):* Defined as daily use of both their allocated e-cigarette and usual cigarettes;
- *General vaping questions (all time points):* Urge to vape, whether they changed devices and/or e-juice; whether they accessed any support for using their e-cigarette (and if so, where and how useful the support was); whether anyone they see at least once a week currently uses an e-cigarette (including whether this is someone they live with or not);
- *Continuation of use (6 and 12 months):* Continued use of their allocated treatment after the end of the treatment period;
- *General health (all time points)*: Self-reported shortness of breath, cough, asthma, COPD, and mental health problems;

Table 2: Details of follow-up

	Call 1			Call 2	Call 3	Call 4	Call 5	Call 6
Timing	**Week 0**			**Quit date (QD)**	**One month after QD**	**Three months after QD**	**Six months After QD**	**12 months After QD**
Description	**Screening (S), Baseline (B), Randomisation (R)**			**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**
General data								
Eligibility criteria	X							
Consent	X							
Age and gender		X						
Height		X						
Weight		X				X	X	X
Ethnicity		X						
Education		X						
Current medication		X		X	X	X	X	X
General health		X		X	X	X	X	X
Pregnancy	X			X	X	X		
Smoking information								
Level of nicotine dependence		X						
Type of tobacco smoked		X						
Pouch size and how long lasts^		X						
Cigarettes smoked per day		X		X	X	X	X	X
Age started		X						
Years smoked		X						
Household smoking		X						

Around others that use e-cigarettes		X				X		
Previous quit attempts & method		X						
Belief in ability to quit		X		X	X			
Any smoking in last seven days				X	X	X	X	X
Any smoking since QD					X	X	X	X
Biochemical verification in those who self-report quitting							X	X
Withdrawal/urge to smoke		X		X	X	X	X	X
Follow-up details								
Quit date			X	X				
Contact details			X	X	X	X	X	X
Treatment allocation and details			X					
Use of non-NRT cessation methods								
Type of cessation method used					X	X	X	X
Intervention period								
Acceptability / perceptions					X	X	X	X
Recommendations					X	X	X	X
Medication compliance				X	X	X		
Other outcomes								
Crossover				X	X	X	X	X
Additional e-cigarette support*				X	X	X	X	X
Dual use				X	X	X	X	X
Cost				X	X	X	X	X
Continuation of allocated treatment							X	X
Side effects/serious adverse events				X	X	X	X	X
Identity*						X	X	X

^ *In people who smoke roll-your-own tobacco* *QD Quit Date* * *In those allocated e-cigarettes*

- *Belief in ability to quit and stay quit (quit date and 1 month):* measured on a scale from 1 to 5 where 1=unlikely and 5=highly likely;
- *Identity (3 and 6 months)*: Whether those allocated e-cigarettes consider themselves a smoker, a smoker still trying to quit, an ex-smoker, an ex-vapor, a vapor trying to quit smoking, a vapor trying to quit vaping, a vapor, other, or none of the above.
- *Perception of their product (1, 3, 6 and 12 months):* Participants' views on use of their allocated treatment as a smoking cessation aid;
- *Recommendations for use (1, 3, 6 and 12 months):* Whether they would recommend their allocated treatment to another smoker who wanted to quit;
- *Occurrence of specific side effects from product use (all time points);* Cough, nausea, dry mouth / throat, redness / swelling at patch site, dizziness, headache, vivid dreams, difficulty sleeping, dry skin, itchiness, other.

- *Serious adverse events (all time points*); Serious adverse events will be recorded and described as per International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, and followed to resolution or stabilisation.
- *Concomitant medication (all time points)*;
- *Cost information:* Cost-per-quitter, cost-per-person reducing their daily cigarette consumption (or when smoking for non-daily smokers) and the incremental cost effectiveness ratio, if the intervention is indeed shown to be more effective than the comparison condition. The tobacco expenditure savings to individual smokers will also be calculated using data on the amount smoked prior to quitting and the price of the particular products smoked.

Sample size

To detect an absolute difference of 8% in six-month continuous abstinence rates between the 21mg nicotine patch + nicotine e-cigarette group and the 21mg nicotine patch + nicotine-free e-cigarette group, 804 participants are needed in each group for 90% power (and 600 for 80% power). To detect an absolute difference of 15% in six month continuous abstinence rates between the 21mg nicotine patch group and the 21mg nicotine patch + nicotine e-cigarette group, 201 participants are needed in each group for 90% power (and 150 for 80% power). A total sample size of 1,809 (804 in both e-cigarette groups and 201 in the nicotine patch group) is needed for 90% power, with p=0.05 and adjusted for 20% loss to follow-up[12] (Figure 1).

<insert Figure 1 here>

A six month quit rate of 16% was assumed for the nicotine patch group, based on the average quit rate observed in the Cochrane review for nicotine patches vs placebo/no NRT control.[14] We estimated a six month quit rate of 31% for the nicotine patch + nicotine e-cigarette group based on the quit rate observed in a trial (n=239) comparing 'nicotine patches plus nicotine spray' against 'nicotine patches plus placebo spray'.[22] A six month quit rate of 23% for the nicotine patch + nicotine-free e-cigarette group was assumed, based on a pragmatic trial (n=1410) undertaken in NZ comparing use of NRT combined with very low nicotine cigarettes.[23] Our previous experience of recruiting smokers from the community suggests recruitment will take 18 months.[12]

Data management

Members of the trial steering committee will provide trial oversight, with day-to-day management of the trial undertaken by the project manager, project coordinator, and data manager. Study data

will be collected by research assistants and directly entered into REDCap (Research Electronic Data Capture), a secure, web-based application hosted at the University of Auckland and designed to support data capture for research studies.[24] All data will be securely stored, regularly backed-up, and retained for 10 years from data-lock. The study will be independently monitored after ten participants have been randomised, at study close-out, and twice during the trial. According to guidelines proposed by Ellenburg et al. (2002) a Data Safety and Monitoring Committee is not required.[25]

Statistical analysis

Analyses will be performed using SAS (9.4) and R.[26] No interim analyses are planned. Analysis will be carried out on an intention-to-treat basis (i.e. all participants as originally allocated after randomisation will be analysed, and all participants lost to follow-up will be assumed to be smoking), with the quit rates, relative risks (RR), absolute risks and 95% CI calculated for the primary and secondary comparison. Treatment groups will be compared using χ^2 tests, with multiple logistic regression analysis adjusting for other variables as appropriate. Sensitivity analyses will be undertaken to determine the impact of using varying cut-offs for CO measurements (i.e. at ≤3ppm, ≤5ppm and ≤8ppm) given lack of consensus about the best reading to use, and secondary analyses performed to correct overall cessation rates for discordance between reported and verified cessation. Sensitivity analyses will also be carried out to determine the effect of missing data. If the level of missing data is >20%, multiple imputation will be employed.[27] A per-protocol analysis will also be performed for the primary outcome where only those participants who completed the treatment originally allocated will be included (i.e. participants with major protocol violations, such as cross-overs treatments, withdrawals, and loss to follow-up will be excluded). The consistency of effects for pre-specified subgroups will be assessed using tests for heterogeneity. Subgroups will be based on age, sex, ethnicity, education, level of nicotine dependence, smoking frequency at baseline (daily/non-daily), and self-efficacy of quitting. Data related to smoking reduction will be reported separately for daily and non-daily smokers. A repeated measures model will be used to analyse change from baseline in cigarettes smoked per day (in non-abstainers), and will adjust for baseline value. Kaplan-Meier curves, the log rank test, and Cox proportional hazards regression analysis will be used to analyse time-to-relapse. Serious adverse events will be defined according to the ICH-GCP E6 guidelines, categorised by the study doctor (masked to intervention product) as definitely, probably, possibly, unlikely, or not related to the intervention, and coded by a medical coder (masked to intervention product) according to ICD-10 AM (8th edition). Events will be analysed by treatment group and

association with study treatment. If the primary outcome of the trial is positive analyses will be undertaken to model the marginal cost-per-quitter, taking a health sector perspective. The tobacco expenditure savings to individual smokers will also be calculated (for those who quit and cut down) to give a more societal perspective on the financial benefits (especially to low-income smokers). For those participants who cut down their tobacco consumption by ≥50%, the cost-per-person reducing their daily cigarette consumption will be calculated.

ETHICS AND DISSEMINATION

Ethics approval was obtained on the 16/09/2015 from the Northern A Health and Disability Ethics Committee (15/NTA/123). Participants are fully informed of their rights to withdraw, the risk/benefits of participating, the confidentiality of their data, and that they may be eligible for compensation from the NZ Accident Compensation Corporation or private health/life insurance should they experience any injury as a result of participating in the trial. Approval from the Standing Committee on Therapeutic Trials was obtained on the 28/09/2015 for use of nicotine e-cigarettes. This study is registered with ClinicalTrials.gov (NCT02521662). The trial dataset will be available from the corresponding author for use in any meta-analyses, on reasonable request. The dissemination plan includes national/international media coverage, publication in a high-impact peer-reviewed journal, and oral presentations to relevant national/international audiences.

DISCUSSION

One of the main limitations of clinical trials designed to prove whether e-cigarettes can help people quit smoking is that their findings are not generalisable, as the studied population is often very different to the general smoking population. For example, trial participants may be paid to participate in an effort to improve compliance, or subpopulations who are less likely to comply are excluded (such as people with mental health or alcohol use problems). This trial was designed to be as pragmatic as possible, with open eligibility and no patient payments (although trial medication was provided at no cost). This design will enable the findings to be more readily generalised to the unique tobacco control environment of NZ, where tobacco is expensive (NZ$25.30, US$18.20, €15.44 as 24/08/17 for a pack of 20 cigarettes), tobacco advertising is banned, point-of-sale display bans are in effect, and cessation support and medication (including combination NRT) is accessible and heavily subsidised. Despite these measures, in 2015 16% of the NZ adult population (≥15 years) were current smokers (14% daily), including 39% of Māori[28] (indigenous NZers who comprise 15% of the population[29]) and 25% of Pacific people[28] (who comprise 5% of the population[29]). Within this environment, information on e-cigarette use by the

population is limited. In 2011/12, a survey of 480 adults (≥ 18 years, smokers and recent quitters) found that 7% had ever purchased e-cigarettes.[30] In 2016, a survey of 3,854 NZ adults (>15 years old, smokers and non-smokers) reported 17% had tried an e-cigarette, 3% were current users (defined as 'used at least daily, weekly or monthly'), and 1% were daily users of e-cigarettes.[31]

The pragmatic nature of the trial is highlighted by our use of a PRECIS-2 (PRagmatic-Explanatory Continuum Indicator Summary-2) wheel.[32] The wheel has nine spokes (or domains) that focus on each aspect of the trial, namely: eligibility, recruitment, setting, organisation, flexibility (delivery of the intervention), flexibility (adherence to the intervention), follow-up, primary outcome, and primary analysis. Each domain is scored on a 5-point Likert scale ranging from 1 "very explanatory" to 5 "very pragmatic". More pragmatic trials have a larger wheel, whilst more explanatory trials have a smaller wheel. The tool also allows the reader to see that certain aspects of a trial may vary along the pragmatic-explanatory continuum. Five authors (NW, MV, TK, VP, CB) independently assessed the design according to the nine domains and the average scores for each domain are indicated on each spoke in Figure 2 (with the range in brackets).

<Insert Figure 2 here>

Current status

Recruitment started on 16th March 2016, with final data collection expected to be completed July 2018. This paper reports on protocol version 4.0, 10th February 2017. The protocol was amended in April 2017, driven by the need to shorten the interview time, reduce participant burden and ensure the trial can finish on budget and on time. The amendments involved removal of the 12-month assessment and several secondary outcomes, namely: smokefree cars/homes (baseline); belief in ability to quit for good (one month); MPSS and urge to smoke (all time-points); general vaping questions (all time-points); general health questions (quit date, one month); perceptions of their allocated product; and recommendations for use (one and six months). Details on the subset of participants that provided data on these removed secondary outcomes will be published. In June 2018 (four years after the trial was designed and funded), the NZ Ministry of Health legalised the sale and supply of nicotine e-cigarettes as consumer products.

AUTHORS' CONTRIBUTIONS

Authorship follows the ICMJE guidelines. NW, VP, GL, ML and CB conceived the original idea for the trial, sought and obtained funding for the trial, and wrote the study protocol. TK is the project manager responsible for the day-to-day running of the trial, whilst MV is the research fellow involved in the trial. VP will undertake all data analyses. This protocol paper was written by MV and NW with input from all co-authors. NW is guarantor for this paper. All authors read and approved the final manuscript.

FUNDING STATEMENT

This trial is funded by a three year project grant from the Health Research Council of NZ (15/202). Approximately NZ$600,000 (€350,000 or US$400,000) was available to run the trial. The e-cigarettes for this trial are being purchased directly from a New Zealand e-cigarette retailer - NZVAPOR. NZVAPOR are not involved in the design, conduct or analysis of the trial, but are providing on-line and phone support to participants regarding use of their allocated e-cigarettes. The e-cigarettes to be used in the trial and NZVAPOR (including the Managing Director) have no links with the tobacco industry. The e-juice for the trial is purchased directly from Nicopharm, Australia. The nicotine patches are supplied by the NZ Government via their contract with Novartis. Nicopharm and Novartis are not involved in the design, conduct or analysis of the trial and have no known links with the tobacco industry. Independent testing of the nicotine content of the e-juice will be undertaken by the NicoTar group at Roswell Park Cancer Institute, Buffalo, New York, USA.

ACKNOWLEDGEMENTS

We thank members of the NZ vaping retailer community for their advice regarding the best type/brand of e-cigarette to use in this trial, plus the best nicotine strength and flavours for the e-juice. We also acknowledge the support of the funder, NZVAPOR, Nicopharm, Dr Maciej Goniewicz, Angela Wadham, and community smoking cessation providers throughout NZ.

COMPETING INTERESTS STATEMENT

No authors have received financial support for the submitted work from any companies with a financial interest in the products under investigation. CB has received benefits in kind (accommodation expenses) from a manufacturer of smoking cessation medications. NW has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation medications (but over five year ago). NW, CB, MV, GL and

VP are currently involved in a clinical trial in which varenicline and matching placebo are supplied by Pfizer under their Investigator-Initiated Research Program. MV has previously undertaken research supported by an unrestricted grant from Pfizer. None of the authors' spouses, partners, or children have financial relationships that may be relevant to the submitted work. All authors have no non-financial interests that may be relevant to the submitted work

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Figure 1: Estimated effect sizes for planned comparisons

Figure 2. Design of the trial along the 'pragmatic to explanatory' continuum

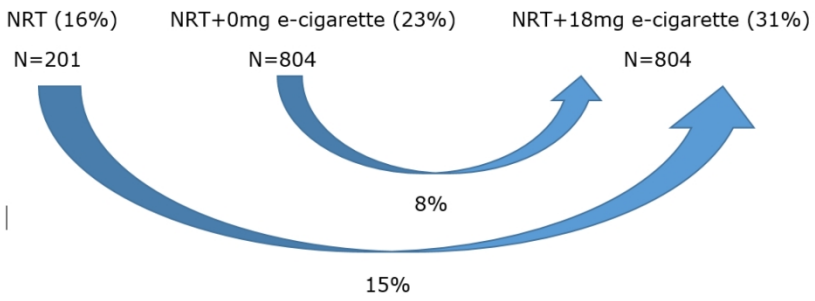

Figure 1: Estimated effect sizes for planned comparisons

296x209mm (300 x 300 DPI)

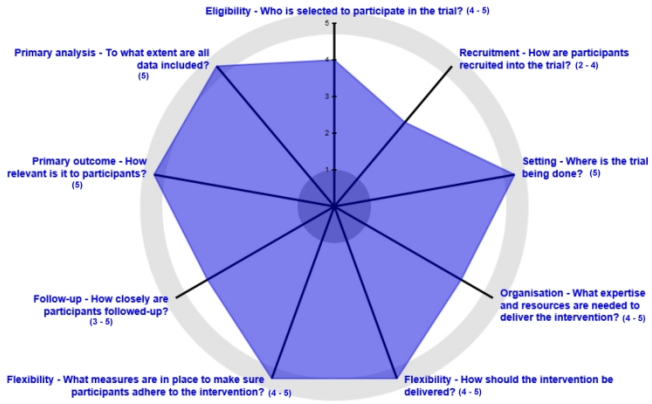

Figure 2. Design of the trial along the 'pragmatic to explanatory' continuum

209x296mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Pg	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
Protocol version	16	Date and version identifier
Funding	18	Sources and types of financial, material, and other support
Roles and responsibilities	1,18	Names, affiliations, and roles of protocol contributors
	N/A	Name and contact information for the trial sponsor
	18	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	14	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	4-6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6-7	Explanation for choice of comparators
Objectives	6	Specific objectives or hypotheses
Trial design	6	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	2,7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	2,7-8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	2,9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	8	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	N/A	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	10-13	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	10-13	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	12	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	13-14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	8	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	8	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	8	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	8	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	8	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	8	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	10-13	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	8	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	14	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	14-15	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	14-15	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	14-15	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	14	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	N/A	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	13,15	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	14	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	15	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	16	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	8	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	N/A	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	15	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	18	Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data	15	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	15	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	18	Authorship eligibility guidelines and any intended use of professional writers
	15	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	-	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	N/A	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.