

BMJ Open 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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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 2 weeks. Participants ($n=1809$), recruited using multi-media advertising, are randomised to 14 weeks of (1) 21 mg nicotine patches ($n=201$); (2) 21 mg nicotine patches+18 mg/mL nicotine e-cigarette ($n=804$); or (3) 21 mg nicotine patches+nicotine free e-cigarette ($n=804$). Participants receive weekly withdrawal-oriented behavioural support calls for 6 weeks post-randomisation. The primary outcome is self-reported biochemically verified continuous abstinence (CA) at 6 months post quit-date. The primary comparison is nicotine patch + nicotine e-cigarette versus nicotine patch + nicotine free 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 6 month CA rates of 8% and 15% respectively). Secondary outcomes, collected by phone interview at quit date, then 1, 3, 6 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 NCT02521662; Pre-results.

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 behaviours (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 6 month abstinence

Table 1 Summary of the design and outcomes from the two published trials of e-cigarettes for 6 month smoking cessation

	ECLAT Caponnetto <i>et al</i>¹¹	ASCEND Bullen <i>et al</i>^{12 13}
Population	Unmotivated to quit	Motivated to quit
Eligibility	≥10CPD for at least 5 years, 18–70 years	≥10CPD 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	7.2 mg e-cigarette (n=100)* 7.2–5.4 mg e-cigarette (n=100)* 0 mg e-cigarette (n=100)* No behavioural support	16 mg e-cigarette (n=289)* 21 mg nicotine patch (n=295) 0 mg e-cigarette (n=73)* Minimal behavioural support
Intervention period	12 weeks	13 weeks (includes 1 week pre-quit)
Follow-up	12 months	6 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 to 5.51 Nicotine e-cigarette: 7.3% Placebo e-cigarette: 5.8% RD=3.16 95% CI –2.29 to 8.61
Smoking reduction	Percentage reduction in CPD at 6 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 6 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 6 months. 0.8 events per person month Nicotine patches: 119 events in 96 participants over 6 months. 0.8 events per person month Placebo e-cigarette: 36 events in 26 participants over 6 months. 0.9 events per person month Nicotine e-cigarette vs Nicotine patches: IRR=1.05, 95% CI: 0.82 to 1.34, p=0.7
Serious adverse events	None reported	None related to treatment

*Ad libitum use.

†Primary outcome.

CPD, cigarettes per day; IRR, incidence rate ratio; RD, risk difference.; CI, confidence interval

outcomes have been published on the use of e-cigarettes for smoking cessation (table 1).^{11–13}

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 (ie, 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 (eg, 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 6 months. Our primary hypothesis is that 21 mg nicotine patches plus 18 mg/mL nicotine e-cigarettes will be more effective at helping smokers quit than 21 mg nicotine patches plus nicotine-free e-cigarettes. Our secondary hypothesis is that a combination therapy (ie, 21 mg nicotine patches plus 18 mg/mL nicotine e-cigarettes) will be more effective than monotherapy (ie, 21 mg 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. While it is logical to include a fourth group (ie, 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 21 mg (24 hours) nicotine patch was selected as it is the standard patch strength used in NZ (Habitrol 21 mg patch, Novartis Consumer Health Australasia Pty). A second generation e-cigarette starter kit (eVOD brand, 1.8 OHM: Kangertech, Shenzhen Guangdong, China) was chosen and purchased from NZVAPOR (<https://www.nzvapor.com/>), with an 18 mg/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 (ie, roll-your-own or factory-made: 38% of NZ smokers use roll-your-own tobacco exclusively¹⁵). The e-liquid (60/40 PG/VG ratio) is sourced from Nicopharm, Australia (<https://www.nicopharm.com.au/>). The e-juice will be independently assessed to verify nicotine content is as labelled, and to check for contaminants. For the nicotine e-liquid, a variability of $\pm 10\%$ 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 2 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 endeavour 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 breast feeding 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 1 week any time in the last year or current users of non-nicotine based cessation therapies (eg, bupropion, clonidine, nortriptyline or varenicline). People are also ineligible if they have any contraindications to nicotine patches (ie, they have had a heart attack, stroke or severe angina within the previous 2 weeks, as per recommendations by the NZ Quitline) or e-cigarette (ie, 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 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 (21 mg nicotine patch alone: 21 mg nicotine patch plus 18 mg/mL nicotine e-cigarette: 21 mg 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:

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

Participants will receive 14 weeks of treatment, consisting of a 2 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 min of telephone-based withdrawal-oriented behavioural support (based on cognitive behavioural therapy) and advice for using their allocated product. All three groups will also receive weekly withdrawal-oriented behavioural support telephone calls (10–15 min) for 6 weeks post-randomisation, delivered by trained smoking cessation advisers. Participants will have their full supply of free nicotine patches plus, if allocated, their free e-cigarette and e-juice (four 30 mL 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) 2 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 titled *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 forward, and continue with their allocated treatment for 12 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 (eg, 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 6 months post quit-date, defined according to the Russell Standard (ie, 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 6 month 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 1, 3, 6 and 12 months post quit-date (table 2).

- ▶ Continuous abstinence (1, 3 and 12 months): the proportion of participants who have stopped smoking, defined as self-report of smoking not more than five cigarettes from the quit date.
- ▶ Seven day point prevalence (all time points): the proportion of participants who have stopped smoking, defined as self-report of having smoked no cigarettes (not even a puff) in the past 7 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 regular smoking (at least 5 cigarettes in the last 7 days).
- ▶ 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 millilitres of juice they use on a typical day (the EVod holds 2.2 ml).
- ▶ 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.
- ▶ 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 participants consider themselves a smoker, a smoker still trying to quit, an ex-smoker, and (in those allocated e-cigarettes) an ex-vaper, a vaper trying to quit smoking, a vaper trying to quit vaping, a vaper, 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

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 7 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
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

Continued

Table 2 Continued

	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
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.

†In those allocated e-cigarettes.

the amount smoked prior to quitting and the price of the particular products smoked.

Sample size

To detect an absolute difference of 8% in 6 month continuous abstinence rates between the 21 mg nicotine patch +nicotine e-cigarette group and the 21 mg nicotine patch +nicotinefree 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 6 month continuous abstinence rates between the 21 mg nicotine patch group and the 21 mg 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 1809 (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-up¹² (figure 1).

A 6 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 6 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 6 month quit rate of 23% for the nicotine patch + nicotinefree 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 10 participants have been randomised, at study close-out and twice during the trial. According to guidelines proposed by Ellenburg *et al*,²⁵ 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 (ie, all participants as originally allocated after randomisation will be analysed,

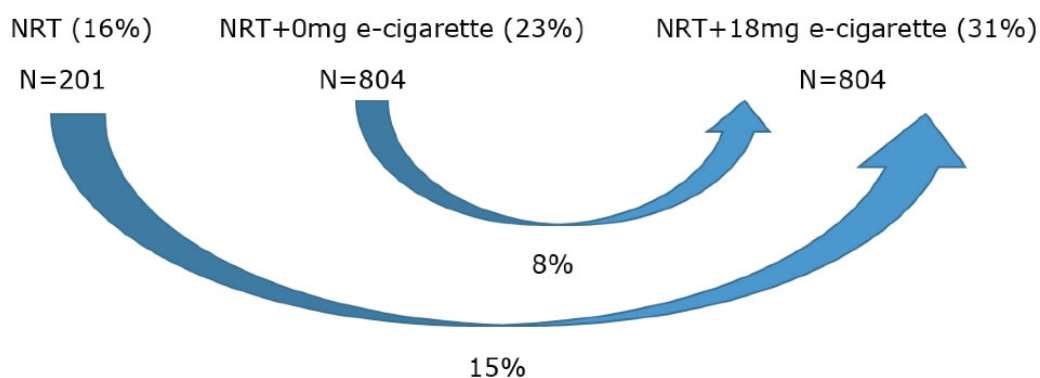


Figure 1 Estimated effect sizes for planned comparisons.

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 (ie, at ≤ 3 ppm, ≤ 5 ppm and ≤ 8 ppm) 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 Complete case analyses will be undertaken for the primary outcome, as well as per-protocol analyses where only those participants who completed the treatment originally allocated will be included (ie, 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 adjusted for baseline will be used to analyse change from baseline in cigarettes smoked per day (in non-abstainers), and change from baseline in weight and Body Mass Index. 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 International Conference on Harmonization-Good Clinical Practice (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 International Classification of Disease, tenth revision, Australian Modification (ICD-10 AM) (eighth 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 $\geq 50\%$, the cost-per-person reducing their daily cigarette consumption will be calculated.

ETHICS AND DISSEMINATION

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 September 2015 for use of nicotine e-cigarettes. 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

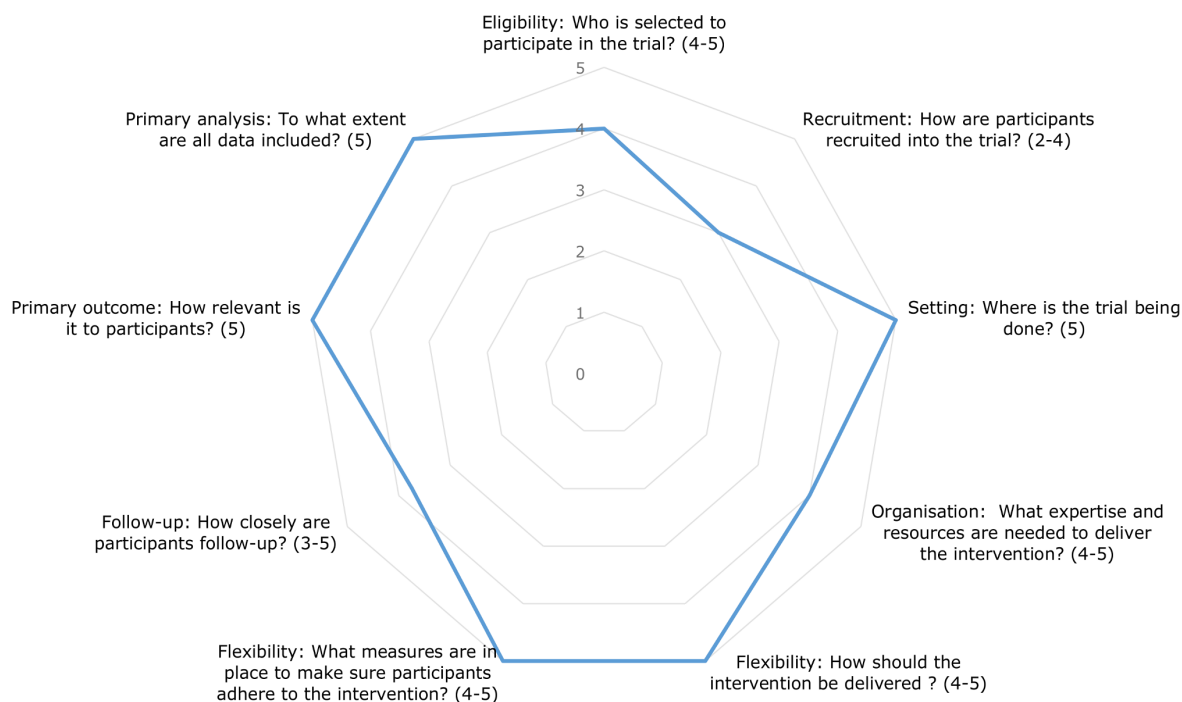


Figure 2 Design of the trial along the 'pragmatic to explanatory' continuum.

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 and/or retention, 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/product 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 August 2017 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 Māori²⁸ (indigenous NZers who comprise 15% of the population²⁹) and 25% of Pacific people²⁸ (who comprise 5% of the population²⁹). Within this environment, information on e-cigarette use by the population is limited. In 2011–2012, 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 3854 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 five-point Likert scale ranging from 1 ‘very explanatory’ to 5 ‘very pragmatic’. More pragmatic trials have a larger wheel, while 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).

Current status

Recruitment started on 16 March 2016, with final data collection expected to be completed July 2018. This paper reports on protocol version 4.0, 10 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 (1 month); MPSS and urge to smoke (all time-points); general vaping questions (all time-points); general health questions (quit date, 1 month); perceptions of their allocated product; and recommendations for use (one and 6 months). Details on the subset of participants that provided data on these removed secondary outcomes will be published. In June 2018 (4 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.

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Contributors 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, while 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.

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Competing interests 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.

Patient consent for publication Not required.

Ethics approval Ethics approval was obtained on the 16/09/2015 from the Northern A Health and Disability Ethics Committee (15/NTA/123).

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