STATISTICAL ANALYSIS PLAN

Final

New Zealand Quit Vaping Study (EQUIT3 Trial)

Trial Registration Number: NCT06832098

21st February 2025

National Institute for Health Innovation

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Study: EQUIT3 trial

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Title: New Zealand Quit Vaping Study (EQUIT3 Trial)

Author: Varsha Parag

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Who else was involved in the discussion of the analysis:
EQUIT3 Steering Committee

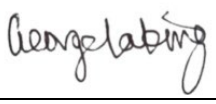
The undersigned have reviewed this document and find it to be consistent with the requirements of the protocol as it applies to their respective areas. The author/reviewer also finds this document to be in compliance with ICH-E9.

21/02/2025

Varsha Parag
Study Statistician — Date

21/02/2025

Natalie Walker
Co-investigator — Date



21/02/2025

George Laking
Principal Investigator — Date

Preface

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed statement of the intended statistical analyses that will be performed in the analysis of data from the study. This document is intended to be stand-alone from the protocol and adhere to the main points in the analysis summary specified in the protocol. However, it is envisaged that the Statistical Analysis Plan can undergo revision outside of the protocol.

It is not anticipated that revisions to the SAP that are in the spirit of the specified protocol analysis would require review by an ethics committee.

It is assumed that the study documentation provided by Data Management follows standard operating procedures. These procedures describe the process for setting up and maintaining study documentation, recording decisions affecting data handling, as well as methods of data capture and the algorithms to ensure accurate data are collected and maintained. It is assumed that the Statistical Analysis Plan will use data from a locked database that has been verified against the clinical record and is a true record of the data collected from the participant. Any data that is missing will be flagged and assumed to be undiscoverable.

The analysis plan will also outline the proposed layout of tables/figures that will be presented.

Scope

Please note that the scope of this SAP is intended to cover ONLY those main analyses described in the protocol. For additional research questions not detailed within this SAP and/or questions requiring further exploratory analyses please refer to other separate SAPs.

To keep within timeframe of issue of Biostatistics report, input into required analysis needs to be pre-specified in this analysis plan. Requests for additional analyses must be minimal after sign-off of this document. This enables all pre-programming programs to be performed ahead of database lock.

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1. STUDY OBJECTIVES

The primary objective of this trial is to evaluate the effectiveness, safety and acceptability of eight weeks of combination NRT plus written behavioural support, compared with an eight-week nicotine tapering programme plus written behavioural support, on six-month vaping abstinence.

Hypothesis: That combination NRT plus written behavioural support will be more effective at helping people quit vaping than combination vape nicotine tapering plus written behavioural support.

2. STUDY DESIGN

Please refer to the study protocol for a full description of the trial design. This is a pragmatic two-arm, parallel group, community-based randomised controlled trial. Recruitment will be undertaken at a national level for a period of 18 months.

Potential participants interested in the trial will register on a trial website. Participants will be asked for on-line consent to complete an online screening questionnaire to determine their eligibility for the trial and verify their phone number. Eligible and interested participants will then provide online consent to enter the trial. A copy of the consent form and participant information sheet will be automatically emailed by the online system to the participant for their records. Participants will also be asked to provide online consent to inform their general practitioner that they are participating in the trial. Baseline data will be collected via the trial website, and then participants will be randomised to either 8 weeks of: 1) combination NRT plus written behavioural support or 2) vape nicotine tapering programme plus written behavioural support.

All interventions will be couriered to participants immediately after randomisation. The courier company will notify the study centre immediately after the courier pack has been delivered, which will initiate the scheduling of follow-up calls. Participants will be asked to begin their treatment the day after they receive their courier pack – this is the designated treatment start date. Note for if there are any participants that do not receive the courier pack, and we are not able to get hold of them after 6 attempts then the designated treatment start date will be put as the day after they should have received their courier pack. Participants will be advised to continue with their allocated treatment, irrespective of any lapses back to vaping (or smoking), with the aim to be vape-free by the end of eight weeks (the designated quit date and end of treatment (EOT). All follow-up calls will be anchored to the EOT regardless of whether they started or completed treatment.

All follow-up information will be assessed over the phone. Outcome assessments will be undertaken at EOT, then one, three- and six-months post EOT.

2.1. Eligibility criteria

Participants will be eligible for inclusion if they:

- Live in New Zealand
- Vape nicotine at least weekly (i.e., one or more days out of the past seven days)
- Are former smokers (i.e. they have smoked tobacco regularly but not at all in the past six months) or never smokers (i.e., they have never been a regular user of smoked tobacco, defined as smoking less than 100 cigarettes in their lifetime)

- Are aged ≥16 years
- Are motivated to quit vaping in the next two weeks,
- Have access to the internet
- Are able to provide consent
- Are a registered patient at a NZ medical facility (GP or community urgent doctors and accident centre).

Participants will be excluded if they:

- Self-report having had a serious cardiovascular event, or hospitalisation for a cardiovascular complaint, in the previous four weeks (e.g. stroke, myocardial infarction, unstable angina, cardiac arrhythmia, coronary artery bypass graft and angioplasty)
- Have uncontrolled hypertension
- Have a strong preference to use/not use NRT or nicotine tapering
- Are current users of smoking cessation pharmacotherapy (e.g. NRT, varenicline, nortriptyline [including if it is used for a different indication], and amitriptyline [as it converts to nortriptyline)
- Are currently enrolled in another vaping cessation programme/trial
- Are current or recent regular smokers
- Have another member of their household taking part in this trial

2.2. Study intervention

Participants allocated to the NRT treatment group will be advised to use the combination NRT (21mg patch plus 1mg mouth spray), with the aim to be vape-free by the end of eight weeks (the designated quit date and EOT). Written instructions as to the use of each product will be provided, along with an explanation of known side effects (e.g., Hiccups for the mouth spray). Daily use of the patches will be recommended, with the mouth spray used to relieve any 'breakthrough' cravings. Advice on reducing use of both products over the eight-week period will also be provided, following the manufacturers guidelines when these products are used for smoking cessation.

Participant are sent 2 boxes of patches which each contain 28 patches (total of 56 patches), and 7 cannisters of mouth spray.

Participants allocated to the nicotine tapering treatment group will be advised to follow a written nicotine tapering plan, with the aim to be vape-free by the end of eight weeks (the designated quit date and EOT). Tapering will be based on their current e-juice nicotine concentration and frequency of vaping upon entry to the trial. Participants will use their own vapes and nicotine e-liquid. People using disposables may find it hard to find disposables with lower nicotine strengths and will be advised to switch to another device for tapering and/or taper by the number of sessions/uses (rather than by nicotine content).

Behavioural support will be given to all participants in the form of a booklet, which will focus on managing the known side effects of nicotine withdrawal, building self-efficacy and relapse prevention.

2.3. Randomisation

All participants who fulfil eligibility criteria will be randomly allocated in a 1:1 ratio to one of the two trial groups using block randomisation using varying block sizes of 2 and 4, and stratified by ethnicity (Māori, non-Māori) and prior smoking status (never-smoker, former-smoker). The randomisation sequence will be generated by the study statistician and loaded into a secure database.

2.4. Sample size

A total of 774 participants (387 per group) will provide 90% power at p=0.05 to detect an absolute difference of 11% in self-reported six-month continuous abstinence rates (vape-free and tobacco-free) between the NRT group and the nicotine tapering group. We have assumed that the self-reported six-month continuous abstinence vaping quit rates (vape-free and tobacco-free) for those in the NRT group will be 26%, compared to 15% in the nicotine tapering group. The sample size accounts for a 28% loss-to-follow-up at six months.

3. STUDY OUTCOMES

3.1. Primary outcome

The primary outcome is being **vape-free and tobacco-free**, defined as self-reported continuous abstinence from vaping at six-months post EOT. Specifically, self-report of no device use (defined as not more than five vaping sessions since EOT), and self-report of no use of any tobacco products (defined as not smoking more than five cigarettes and no use of any other tobacco products from EOT). Individuals may or may not be using NRT.

The primary outcome will be partially validated. There is no vaping-specific biomarker available, so verification of ‘vape-free’ status can’t be validated. However, tobacco-free status will be verified using exhaled carbon-monoxide (CO) measurement with a Bedfont Smokerlyzer (≤5 ppm signifying abstinence). We will visit all participants in the greater Auckland region who claim they are vape-free and tobacco-free, to verify their tobacco-free status in a face-to-face meeting. If participants are not tobacco-free, they will be referred to a community-based smoking cessation provider, their GP, or Quitline for smoking cessation support. For participants outside of Auckland who self-report that they are vape-free and tobacco-free, we will provide their contact details (with their consent) to their region’s community-based smoking cessation service, so that the service can undertake the in-person visit to collect the CO measurement on our behalf (CO measurements are standard care for these providers). If participants are not tobacco-free, the community-based smoking cessation provider will be able to immediately provide smoking cessation support. All CO findings will be extrapolated to the full sample, to account for those people living in areas without available smoking cessation providers.

3.2. Secondary outcomes

The following secondary outcome measures will be assessed in all participants at EOT then at one, three and six post EOT (unless otherwise stated). Note all outcomes at EOT will be based on the last 8 weeks (since the treatment start date which is the day after the participant received their courier pack).

- **Vape-free and tobacco-free self-reported continuous abstinence:** defined as no device use (not vaping more than five vaping sessions since EoT) and no use of any tobacco products (not smoking more than five cigarettes and no use of any other tobacco products since EoT), but may or may not be using NRT
- **Vape-free and tobacco-free self-reported 7-day point prevalence abstinence**: defined as no device use and no use of any tobacco products, not even a single puff/use in the previous seven days, but may or may not be using NRT
- **Vape-free self-reported continuous abstinence**: no device use i.e. not vaping more than five vaping sessions since EoT, but may or may not be using tobacco products and/or NRT
- **Vape-free self-reported 7-day point prevalence abstinence**: no device use (not even a single puff) in the previous seven days, but may or may not be using tobacco products and/or NRT
- **Nicotine-free verified six-month continuous abstinence**: defined as not vaping nicotine (not vaping nicotine more than five vaping sessions since EoT), not using any tobacco products (not smoking more than five cigarettes and no use of any other tobacco products since EoT), and not using any NRT since the EoT.

  This will be verified using salivary cotinine (an established marker for nicotine from NRT, vapes and tobacco) where a reading of ≤10 ng/ml signifies abstinence. Saliva samples will be collected from participants in the greater Auckland region who claim they are nicotine-free. Findings from the saliva tests will be extrapolated to the full trial sample.
- **Nicotine-free self-reported continuous abstinence** (post-EoT only): defined as not vaping nicotine (not vaping nicotine more than five vaping sessions since EoT), not using any tobacco products (not smoking more than five cigarettes and no use of any other tobacco products since EoT), and not using any NRT since the EoT.
- **Nicotine-free self-reported 7-day point prevalence abstinence** (post-EoT only): defined as not vaping nicotine, not using any tobacco products (not even a single puff/use), and not using any NRT in the previous seven days;
- **If vaping:** Details on frequency (number of vaping sessions per day on average) and nicotine use (strength, freebase or salt), and flavours currently used.
- **Lapse/relapse back to vaping:** Time to first lapse back to vaping will be defined as time to first use of a vape from EOT, even a single puff. Time to first relapse will be defined as time to vaping more than five sessions a day for three or more days in a row from EOT.
- **Relapse back to smoking in former smokers**, including time to first lapse (defined as time to first cigarette from EOT, even a single puff) and time to first relapse (time to smoking more than five cigarettes a day for three or more days in a row), and cigarettes per day;
- **Smoking initiation in never-smokers:** smoking in the last 7 days. If yes, frequency of smoking (daily/non-daily). If daily, cigarettes per day.
- **Engagement with treatment:** measured at EoT. In the NRT group engagement will be defined as use of their allocated interventions (patches and/or mouth spray) at least once during first two weeks. Engagement in the

tapering group will be defined as reading and/or using the tapering plan at least once in the first two weeks.

- **Treatment use**: Use of their allocated product, measured at EoT. Participants allocated NRT will be asked to provide a count of how much of the provided NRT they still have at EOT. Both groups will be asked about use of their allocated intervention at least once in the last 8 weeks (during the intervention period).
- **Other vaping cessation support**: Participants will be asked if they seek out other vaping cessation support, such as use of an app, Quitline, etc.
- **Change from baseline in signs and symptoms of nicotine withdrawal and urge to vape**: Measured using the MPSS.
- **Crossover:** Participants in the nicotine reduction group will be asked whether they accessed and used nicotine patches and/or mouth spray during the trial, and if so, at what time during the trial and what product/type they used. Participants in the nicotine reduction group will also be asked if they used other forms of NRT such as nicotine gum, lozenges, etc during the trial. Participants in the NRT group will be asked if they followed their own tapering plan during the trial.
- **Acceptability of the allocated intervention**: Participants will be asked at EOT for their views on the use of their allocated intervention as a cessation aid (i.e., what they liked or disliked).
- **Recommendations**: Participants will be asked at EOT whether they would recommend their allocated treatment to another vaper who wanted to quit.
- **Continuation of intervention:** Defined as continued use of their allocated treatment post EOT. And participants in the NRT group will also be asked if they used other forms of NRT such as nicotine gum, lozenge, etc.
- **Cannabis use (at six months only):** Participants will be asked how often they have used cannabis in the past six months (never, monthly or less, 2-4 times a month, 2-3 times a week, 4 or more times a week). This question is from the revised Cannabis Use Disorders Identification Test (CUDIT-R).
- **Change from baseline in alcohol use (at six months only):** will be measured using the AUDIT-C.
- **Change from baseline in body mass index:** Self-reported weight will be asked to determine change in body mass index from baseline.
- **Change in health state**: Change from baseline in shortness of breath, cough, asthma, chronic pain, COPD, or mental health. Development of, or change in, health conditions related to listed precautions.
- **Serious adverse events (SAEs)**: Participants will be asked about any new, unusual, unexpected serious health events during or since starting treatment, and whether they felt they were related to treatment. Only self-reported SAEs will be recorded given the well-known safety profile for NRT. We will seek Māori/Pacific perspectives on what they consider SAEs.
- **HRQoL** will be measured using the New Zealand EQ-5D-5L. As part of our duty of care, after answering the questions about anxiety and depression participants will be reminded of the confidential support services available for depression and anxiety.
- **Cost outcomes:** Cost-per-quitter, cost-per-person reducing their daily vaping consumption, and the incremental cost-effectiveness ratio.

At each follow-up call, women will be asked if they have become pregnant since enrolling in the trial. All women who are pregnant at follow-up will be asked to discuss their on-going use of their allocated treatments with their GP or lead maternity caregiver.

4. DATA SOURCES

Data collected from the following EQUIT3 case report forms and questionnaires which will be extracted from the NIHI Redcap database into SAS for the analyses:

- Form A1: Consent for screening
- Form A2: Screening and eligibility
- Form A3: Second consent
- Form B: Baseline
- Form M: Medications
- Form R: Randomisation
- Form T: Trial treatment
- Form C0: End of treatment (EoT)
- Form C1: One month post EoT
- Form C3: Three month post EoT
- Form C6: Six month post EoT
- Form V: Verification
- Form X: Serious adverse events

5. VARIABLE DEFINITIONS

The following definitions relate more specifically to the derived variables and non-standard definitions required for analysis of the data that are specific to the analyses referred to throughout this SAP. Please refer to the study protocol for a complete list of abbreviations set out for this study.

Note outcomes at EOT (collected in form C0) will be based on the last 8 weeks (since the treatment start date which is the day after the participant received their courier pack).

- Time between designated treatment start date and actual vaping quit date (from form C0 question 1.07)
- **Use of cigarettes and other tobacco combined**: For each form C the following will be coded:
    - Used cigarettes: question 3.01 (smoked any cigarettes since EoT) =Yes
    - Used other tobacco products: question 3.08 (used any other tobacco products since EoT) =Yes
    - Combined cigarettes and other tobacco (based on above 2 variables):
        - Neither cigarette or other tobacco
        - Cigarette use only
        - Other tobacco use only
        - Both cigarettes and other tobacco

- **Continuous abstinence**: For each form C the following self-reported continuous abstinence variables will be coded. Continuous abstinence will be defined for vaping as not vaping more than five vaping sessions in total since EoT, and for smoking as not smoking more than five cigarettes in total and no use of any other tobacco products since EoT.

  Note if previous follow-up form C's (except form C0) state they used more than 5 since EoT then subsequent follow-ups will be set to Not quit. Also, if a follow-up form is missing but the subsequent follow-up form(s) says they had less than 5 since EoT (and no other previous follow-up forms have said they had more than 5 since EoT), then the missing follow-up form will have continuous abstinence set to 'Quit'.

  - **Vape-free continuous abstinence** coded as:
    - Yes if question 2.01 (vaped since EoT)=None or ≤ 5 vaping sessions
    - No if question 2.01='Yes, more than 5 vaping sessions'
    - Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or question 2.01=missing
  - Tobacco-free continuous abstinence coded as:
    - Yes if question 3.01 (smoked any cigarettes since EoT)=None or ≤ 5 cigarettes and question 3.08 (used any other tobacco products since EoT)=No
    - No if questions 3.01='Yes, more than 5 cigarettes' question and/or 3.08=Yes
    - Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or questions 3.01 or 3.08 are missing
  - **Vape-free and tobacco-free continuous abstinence** coded as (in italics):

		Tobacco-free continuous abstinence		
		Missing	No	Yes
Vape-free continuous abstinence	Missing	*Missing*	*No*	*Missing*
	No	*No*	*No*	*No*
	Yes	*Missing*	*No*	*Yes*

    For participants that have vape-free and tobacco-free continuous abstinence equal to 'Quit' at six months, biochemical verification will be assessed using an exhaled CO measurement of ≤ 9 ppm. Biochemical verification of abstinence will be set to Yes where form V (Verification) question 3.15 ≤ 9 ppm, and it will be set to No where form C 6 month question 2.02 > 9 ppm. Reasons for not having a CO measurement in quitters will also be reported (question 2.01a).

  - Nicotine vape-free continuous abstinence post-EoT coded as:
    - Yes if:
      - question 2.01 (vaped since EoT)=None or ≤ 5 vaping sessions
      - OR questions 2.01='Yes, More than 5 vaping sessions' and 2.10 (nicotine strength)=0mg only

- No if questions 2.01=’Yes, More than 5 vaping sessions’ and 2.10 is ≥1mg or equal to ‘There is nicotine in the vape, but I don't know the strength’
- Missing if question 1.03 (assessment outcome) is not equal to ‘Information available’ or question 2.01=missing or question 2.10=missing/I don’t know (where questions 2.01=Yes)

- Nicotine vape-free and tobacco-free continuous abstinence post-EOT coded as (in italics):

		Tobacco-free continuous abstinence		
		Missing	No	Yes
Nicotine vape-free continuous abstinence	Missing	*Missing*	*No*	*Missing*
	No	*No*	*No*	*No*
	Yes	*Missing*	*No*	*Yes*

- NRT-free continuous abstinence post-EoT coded as:
  - In the Nicotine tapering group:
    - Yes if question 5.01 (Other than the products sent, have you used any nicotine products since EoT) is not equal to Nicotine patch, mouth spray, gum, lozenge, or other (specified as containing nicotine)
    - No if question 5.01=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)
    - Missing if question 1.03 (assessment outcome) is not equal to ‘Information available’ or 5.01=missing
  - In the NRT group:
    - Yes if questions 4.01 (Since EOT have you used the patch and the mouth spray that we provided to you)=No, AND 5.01 is not equal to Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)
    - No if question 4.01=Yes, OR question 5.01=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)
    - Missing if question 1.03 (assessment outcome) is not equal to ‘Information available’ or questions 4.01 or 5.01 are missing

- **Nicotine-free continuous abstinence** post-EoT coded as (in italics):

		NRT-free continuous abstinence		
		Missing	No	Yes
Nicotine vape-free and tobacco-	Missing	*Missing*	*No*	*Missing*
	No	*No*	*No*	*No*

free continuous abstinence	Yes	*Missing*	*No*	*Yes*

For participants that have nicotine-free continuous abstinence equal to 'Quit' at six months, verification will be assessed using salivary cotinine. Saliva samples will be collected from participants in the greater Auckland region who claim they are nicotine-free. This will be verified using salivary cotinine where a reading of ≤10 ng/ml signifies abstinence. Reasons for not having a saliva sample in participants who are nicotine-free will also be reported.

- **Seven-day point prevalence**: For each form C the following self-reported 7-day point prevalence variables will be coded.
  - **Vape-free 7-day point prevalence** (no device use, not even a single puff in the previous 7 days) coded as:
    - Yes if question 2.01 (vaped since EoT)='None', or question 2.01=Yes and question 2.03 (vaped in last 7 days)='No, not even a puff'
    - No if questions 2.01=Yes and 2.03=Yes
    - Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or questions 2.01 or 2.03 are missing
  - Tobacco-free 7-day point prevalence (no use of any tobacco products, not even a single puff/use in the previous seven days) coded as:
    - Yes if:
      - question 3.01 (smoked any cigarettes since EoT)='None', or questions 3.01=Yes and 3.03 (smoked any cigarettes in last 7 days)='No, not even a puff'
      - AND question 3.08c (using any other tobacco products in the last 7 days)=No
    - No if questions 3.01=Yes and 3.03=Yes, OR question 3.08c=Yes
    - Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or questions 3.01, 3.03 or 3.08c are missing
  - **Vape-free and tobacco-free 7-day point prevalence** (no device use and no use of any tobacco products, not even a single puff/use in the previous 7 days) coded as (in italics):

		Tobacco-free 7-day point prevalence		
		Missing	No	Yes
Vape-free 7-day point prevalence	Missing	*Missing*	*No*	*Missing*
	No	*No*	*No*	*No*
	Yes	*Missing*	*No*	*Yes*

  - Nicotine vape-free 7-day point prevalence (no nicotine device use, not even a single puff/use in the previous 7 days) post-EOT coded as:
    - Yes if:
      - question 2.01 (vaped since EoT)='None'

- OR question 2.01=Yes and question 2.03 (vaped in last 7 days)='No, not even a puff'
- OR questions 2.01=Yes and 2.03=Yes and 2.10 (nicotine strength)=0mg only

  - No if questions 2.01=Yes and 2.03=Yes and 2.10 is ≥1mg or equal to 'There is nicotine in the vape, but I don't know the strength'
  - Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or question 2.01=missing or question 2.10=missing/I don't know (where questions 2.01=Yes and 2.02=Yes)

- Nicotine vape-free and tobacco-free 7-day point prevalence (no nicotine device use and no use of any tobacco products, not even a single puff/use in the previous 7 days) post-EOT coded as (in italics):

		Tobacco-free 7-day point prevalence		
		Missing	No	Yes
Nicotine vape-free 7-day point prevalence	Missing	*Missing*	*No*	*Missing*
	No	*No*	*No*	*No*
	Yes	*Missing*	*No*	*Yes*

- NRT-free 7-day point prevalence (i.e not using any NRT in the previous 7 days) post-EOT coded as:
  - In the Nicotine tapering group:
    - Yes if:
      - question 5.01 (Other than the products sent, have you used any nicotine products since EoT) is not equal to Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)
      - OR (questions 5.01=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)) and 5.01c (Have you used any of these nicotine products (patches, mouth spray, gum, lozenges) in the last 7 days)=No and 5.01e (Have you used any of the other nicotine product in the last 7 days)=No [if Other is specified as containing nicotine]
    - No if question 5.01=Nicotine patch, mouth spray, gum lozenge or other (specified as containing nicotine) and (5.01c=Yes or 5.01e=Yes [if Other is specified as containing nicotine])
    - Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or questions 5.01 or 5.01c or 5.01e are missing
  - In the NRT group:
    - Yes if:
      - question 4.01 (Since EOT have you used the patch and the mouth spray that we provided to you)=No AND 5.01 is not equal

to Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)

- OR questions 4.01=Yes and 4.02 (Have you used the patch and the mouth spray that we provided to you in the last 7 days)=No AND 5.01=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine) and 5.01c (Have you used any of these nicotine products (patches, mouth spray, gum, lozenges) in the last 7 days)=No and 5.01e (Have you used any of the other nicotine product in the last 7 days)=No [if Other is specified as containing nicotine]
- OR questions 4.01=No and 5.01= Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine) and 5.01c=No and 5.01e=No [if Other is specified as containing nicotine]
- OR questions 4.01=Yes and 4.02=No and 5.01 not equal to Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine)

- No if:
  - Question 4.01=Yes and 4.02=Yes
  - OR question 5.01=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine) and (5.01c=Yes or 5.01e=Yes [if Other is specified as containing nicotine])
- Missing if question 1.03 (assessment outcome) is not equal to 'Information available' or questions 4.01, 4.02, 5.01, 5.01c or 5.01e are missing

- **Nicotine-free 7-day point prevalence** (not vaping nicotine, not using any tobacco products (not even a single puff/use), and not using any NRT in the previous 7 days) post-EOT coded as (in italics):

		NRT-free 7-day point prevalence		
		Missing	No	Yes
Nicotine vape-free and tobacco-free 7-day point prevalence	Missing	*Missing*	*No*	*Missing*
	No	*No*	*No*	*No*
	Yes	*Missing*	*No*	*Yes*

- **Time to first lapse back to vaping:** at 6 month follow-up will be created where:

  event = first lapse (return to vaping i.e. have first puff of a vape) where the first form C (1, 3 and 6 months) with questions 2.01 (vaped since EoT) =Yes a few puffs, or more

  duration = days since EoT to date of first lapse in form C question 2.02

  Participants that withdraw will be censored on the last available visit, and participants that have not lapsed by the 6 month follow-up will be censored on the 6 month visit date. Note the first form C follow-up visit with a lapse date will

be taken since this will be more accurately remembered by participants than later visits.

- **Time to first relapse back to vaping:** at 6 month follow-up will be created where:

  event = first relapse (vaping more than five sessions a day for three or more days in a row) where the first form C (1, 3 and 6 months) with question 2.06 = Yes

  duration = days since EoT to date of first relapse in form C question 2.07

  Participants that withdraw will be censored on the last available visit, and participants that have not relapsed by the 6 month follow-up will be censored on the 6 month visit date. Note the first form C follow-up visit with a relapse date will be taken since this will be more accurately remembered by participants than later visits.

- **Time to first lapse back to smoking in former smokers:** at 6 month follow-up will be created for participants that said they were former smokers at baseline (form B question 6.01=I used to smoke tobacco, but don't now) where:

  event = first lapse (return to smoking i.e. have first puff of a cigarette) where the first form C (1, 3 and 6 months) with question 3.01 (smoked cigarettes since EoT)= Yes a few puffs, or more

  duration = days since EoT to date of first lapse in form C question 3.02

  Participants that withdraw will be censored on the last available visit, and participants that have not lapsed by the 6 month follow-up will be censored on the 6 month visit date. Note the first form C follow-up visit with a lapse date will be taken since this will be more accurately remembered by participants than later visits.

- **Time to first relapse back to smoking in former smokers:** at 6 month follow-up will be created for participants that said they were former smokers at baseline (form B question 6.01=I used to smoke tobacco, but don't now) where:

  event = first relapse (smoking more than five cigarettes a day for three or more days in a row) where the first form C (1, 3 and 6 months) with question 3.06 = Yes

  duration = days since EoT to date of first relapse in form C question 3.07

  Participants that withdraw will be censored on the last available visit, and participants that have not relapsed by the 6 month follow-up will be censored on the 6 month visit date. Note the first form C follow-up visit with a relapse date will be taken since this will be more accurately remembered by participants than later visits.

- **Engagement with treatment**: measured at EoT. Engagement in the NRT group will be defined as use of their allocated interventions (patches and/or mouth spray) at least once during first two weeks. Engagement in the tapering group will be defined as reading and/or using the tapering plan at least once in the first two weeks.
  - In the NRT group engagement for patches and/or mouth spray will be coded as Yes using form C0 if question 4.02 (date started patches) is in first 2 weeks OR question 4.07 (date started mouth spray) is in first 2 weeks

- In the nicotine tapering group engagement will be coded as Yes using form C0 if question 4.12 (date started nicotine tapering plan) is in first 2 weeks

- **Treatment use**: Use of their allocated product, measured at EoT.

  The amount of NRT used in the NRT group will also be summarised based on how much of the provided NRT the participant still has at EOT.

  The following questions on the number of patches left from form C0 will be used for this:

  - Whole supply (question 4.04a). Note participants are sent 2 boxes of patches which each contain 28 patches (total of 56 patches).
  - How many full boxes (question 4.04b)
  - How many patches (question 4.04c)

  And the following questions on the number of mouth spray bottles left from form C0 will be used for this:

  - Whole supply (question 4.09a), if they have not used any of the spray. Note participants are sent 7 cannisters of mouth spray.
  - How many full cannisters (question 4.09b)
  - How many partial cannisters (question 4.09c)

  And use of the allocated product at least once during the eight week treatment period will also be summarised by each group.

- **Other vaping cessation support:** from form C's questions 5.01 (other than the products sent, have you used any nicotine products since EoT) and 5.02 (other than the products sent, have you used anything else since EoT).

- **Signs and symptoms of nicotine withdrawal and urge to vape**: Measured using the MPSS which consists of the following:

  - 5-point ratings of depressed mood, irritability, restlessness, hunger and difficulty concentrating. MPSS score calculated by summing all 5 items (range 5 to 25).
  - 6-point ratings of time spent with urges to vape and strength of urges to vape. Note the strength of urges question has values 1 to 5. And participants that tick 'Not at all' for time spent with urges to smoke question have to then skip to next section of questions and don't answer question on strength of urges. So for these participants need to set strength of urges to equal value 0. [Therefore, this question will then have values 0 to 5]. Urge score calculated by summing the two urges questions and will have range 0 to 10.

- **Cross-over**: from form C's where:

  - In the nicotine reduction group where participants said they used nicotine patches and/or mouth spray during the trial, where question 5.01 (other than the products sent, have you used any nicotine products since EoT) = Nicotine patch or mouth spray. If yes, questions 5.01a to 5.01b contain when they started.
    - Also separately looking at participants in the nicotine reduction group who said they used any form of NRT during the trial, where question 5.01 = Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine).

- In the NRT group where question 5.02 (other than the products sent, have you used anything else since EoT) = I used my own tapering plan.

- **Continuation of intervention**:
  - Continued use of their allocated treatment where:
    - Form C0 where question 4.03 (still using patches)=Yes or question 4.08 (still using mouth spray)=Yes or question 6.01 (other than the products sent, have you used any nicotine products since treatment start date)=Nicotine patch or mouth spray (in the NRT group), or question 4.13 (still using nicotine tapering plan)=Yes (in the nicotine tapering plan group).
    - Forms C1 to C6 where question 4.01 (Since EOT have you used the patch and the mouth spray that we provided to you)=Yes or question 5.01 (other than the products sent, have you used any nicotine products since EOT)=Nicotine patch or mouth spray (in the NRT group), or question 4.03 (Since EOT have you used the nicotine tapering plan we provided to you)=Yes (in the nicotine tapering plan group).
  - Also for the NRT group separately looking at participants that continued using their allocated treatment and including other forms of NRT:
    - Form C0 where question 4.03 (still using patches)=Yes or question 4.08 (still using mouth spray)=Yes or 6.01 (other than the products sent, have you used any nicotine products since treatment start date)=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine).
    - Forms C1 to C6 where question 4.01 (Since EOT have you used the patch and the mouth spray that we provided to you)=Yes or 5.01 (other than the products sent, have you used any nicotine products since EOT)=Nicotine patch, mouth spray, gum, lozenge or other (specified as containing nicotine).

- **Cannabis use:** will be measured at baseline and 6 months only, where participants will be asked how often they have used cannabis in the past six months (never, monthly or less, 2-4 times a month, 2-3 times a week, 4 or more times a week). This question is from the revised Cannabis Use Disorders Identification Test (CUDIT-R). This will be dichotomised to never used and have used cannabis in the past six months.

- **Alcohol use:** will be measured using the Alcohol Use Disorders Identification Test (AUDIT-C) at baseline and 6 months only.

  AUDIT-C score will be calculated by summing all three items and will have a range 0 to 12 with higher scores indicating a greater risk of alcohol dependence. Note for those participants that tick ‘Never’ for the first AUDIT-C item (How often do you drink alcohol in the past year) then skip the next two AUDIT-C items, so for these AUDIT-C score to be set to value 0.

  For men, an AUDIT-C score ≥ 4 indicates an increased risk of hazardous drinking or alcohol dependence, while in women it is a score of ≥ 3. An AUDIT-C score ≥ 8 indicates a very high risk for both men and women.

6. BIOSTATISTICS QUALITY ASSURANCE

Well in advance of study data-lock, programming across all analyses will commence with dummy data. This will allow sufficient time to turn around the 'real' analyses as quickly as possible. Early programming will also allow for a preliminary run at merging of the various datasets into the correct data structure required for analysis. Specifically, the datasets in section 4 will be taken before data-lock and passed through the necessary biostatistical processes (which will include checking that all the datasets have been imported correctly into SAS and are all able to be correctly merged together).

7. ANALYSIS POPULATIONS

7.1. Intention to Treat

All treatment evaluations will be performed on the principle of 'Intention To Treat' (ITT) unless otherwise specified. The ITT population will consist of all randomised participants regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol.

7.2. Per Protocol

A per protocol analysis will also be performed on the primary outcome in order to check the robustness of the results. The criteria for defining the per protocol population will include consideration of the following: do not have important protocol violations, do not have missing outcome data (e.g. due to lost to follow-up, withdrawals), were exposed to the intervention as planned (i.e. used only assigned intervention and did not cross-over), those who have engaged with the treatment allocated.

An important protocol violation will be defined as a violation that may impact participant safety, affect the integrity of trial data, affect the participant's willingness to participate in the trial, and serious discrepancy resulting from error, fraud or misconduct. For example, failure to obtain informed consent, breach of randomisation procedures or allocation concealment, and randomisation of participants who do not meet inclusion/exclusion criteria.

8. STATISTICAL ANALYSIS

All statistical analyses will be performed using SAS version 9.4 and R version 4.2.3. Data collected in the NIHI Redcap database will be extracted into SAS for the analyses. All statistical tests will be two-tailed and a 5% significance level throughout the analyses. No adjustments for multiplicity are planned for any of the outcomes. Interim analyses will only be undertaken as part of the requirements for the Data Monitoring Committee if needed.

Summaries of continuous variables will be presented as means and standard deviations (or medians and inter-quartiles for severely skewed data), while categorical variables will be presented as frequencies and percentages. Continuous variables will be compared with t-tests (or Mann-Whitney tests) and categorical data with chi-squared tests as appropriate.

A separate EXCEL file containing the SAP tables specific to this study will be provided based on all the analyses stated below (see Appendix I).

8.1. CONSORT statement

All participants who were invited to participate in this study should be accounted for and a CONSORT statement is prepared and flow chart prepared as Figure 1 for the main paper. The reasons for non-participation will be discussed in relation to the external validity of the study and the pattern of protocol violations considered as potential sources of bias. Reasons for early withdrawal will be listed for all participants that prematurely discontinued intervention or the study. The number of participants that were registered but not randomised will also be presented.

8.2. Participant accountability

Tables describing participant accountability will be produced. The number of participants who were registered, fulfilled eligibility criterion, together with reasons for exclusion will be summarised. The status of participants at each follow-up visit, and the number of protocol violations will also be summarised.

8.3. Baseline characteristics

Baseline variables will be summarised for each treatment group. Since any differences between the groups at baseline could only have occurred by chance, no formal significance testing will be conducted.

8.4. Concomitant medications

Concomitant medications (coded to the Anatomical Therapeutic Chemical, ATC, classification system) by number of events and people will be summarised for each intervention group. Separate tables will be given for general ATC categories, and for the detailed ATC codes.

8.5. Primary outcome analysis

The proportion of participants that have been biochemically verified as continuously abstinent (vape-free and tobacco-free) at six months by group will be analysed using log-binomial regression, and the risk in each group, relative risks, absolute risk differences, and corresponding 95% confidence intervals will be calculated. All analyses for the primary outcome will be ITT (unless otherwise stated) and include all randomised participants. Missing outcomes will be imputed using multiple imputation assuming the data is missing at random. Multiple imputed datasets will be created (n=50) and the imputation model will include baseline age, gender, and group, and the fully conditional specification logistic regression method will be used to impute the missing outcomes. The imputed datasets will be analysed using log-binomial regression and combined to output one inference. Adjusted analyses for potential covariates will be conducted if needed.

To check the robustness of the primary outcome the following sensitivity analyses will be conducted:

- self-reported continuous abstinence at 6 months (not biochemically verified)
- using the following varying cut-offs used for CO measurements: ≤ 3 ppm, ≤ 5 ppm, ≤ 8 ppm

The following sensitivity analyses will also be conducted for the primary outcome where groups will be compared using chi-squared tests:

- complete case analysis
- per protocol analyses where the following participants will be excluded: have important protocol violations (see 7.2), missing primary outcome data (due to lost to follow-up, withdrawals, etc), and cross-over treatments

- if there is sufficient data the same per protocol analyses as above plus will be conducted but also excluding participants that had no engagement with their allocated product (did not use at least once in the first two weeks)

Tests for heterogeneity will be used to examine if there is any difference in the groups on the unadjusted primary outcome for the following subgroups (if there is sufficient data):

- baseline age (will be dichotomised based on the median)
- gender
- ethnicity (Māori, non-Māori)
- education (<12 years of attending school, ≥12 years of attending school)
- smoking history (never smoked, former smoker)
- baseline cannabis use (will be categorised based on the data)
- alcohol use (for men, an AUDIT-C score ≥ 4 indicates an increased risk of hazardous drinking or alcohol dependence, while in women it is an AUDIT-C score of ≥ 3)
- history/current mental health status (form B questions 8.01 [Have you in the past ever received medical treatment] and 8.02 [Are you currently receiving medical treatment] both put as “None” vs all others)
- vaping dependence (will be dichotomised based on the median)
- frequency of vaping (daily where form question B 3.05 (In the last 7 days how often did you vape)=everyday, vs all others)
- device type (will be categorised based on the data)
- motivation to quit (will be categorised based on the data)
- pain (yes where form B question 8.05 (Do you experience chronic pain)=Yes, vs all others).
  [Note if there is not sufficient data for pain then a general health issue will be coded where it is Yes to any of the following: shortness of breath, cough, asthma, chronic pain, COPD, or mental health]

A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term in the main regression analyses.

In the event of a null result in the main analysis of the primary outcome, we will calculate a Bayes Factor (BF) to differentiate between evidence for the hypothesised effect, no effect, and data insensitivity. We will use a half-normal distribution, the mode at 0 (no effect), and the standard deviation equal to the hypothesised effect size used in the sample size calculation (OR~2.0; https://harry-tattan-birch.shinyapps.io/bayes-factor-calculator/). BFs >3 can be interpreted as evidence that the effect is more likely than the null, BFs <1/3 as evidence that the null is more likely than the effect, and BFs between 1/3 and 3 suggest the data are insensitive to distinguish the effect from the null.

8.6. Secondary outcomes analysis

Descriptive summary statistics for each follow-up visit and treatment group will be presented for all secondary outcomes. For all secondary outcomes (unless otherwise stated) participants with missing outcome data will be excluded from the analyses.

Incidence rates, risk difference, relative risks and 95% confidence intervals will be calculated for all continuous abstinence and seven-day point prevalence abstinence secondary outcomes at each follow-up visit. Both complete case analysis and ITT analysis (where missing outcomes will be imputed using the same multiple imputation method described above for the primary outcome) will be

conducted. Dichotomised cannabis use at 6 months will be compared using logistic regression and will include group and the baseline measure in the model.

The change from baseline in the AUDIT-C score at 6 months will be analysed using linear regression and include the baseline measure in the model. The change from baseline in each of the repeated continuous outcomes (BMI, withdrawal) will be analysed using mixed models. Each model will include group and the baseline measure. The withdrawal analyses will be include 6-month continuous abstainers only where separate models will be conducted defining abstainers as vape-free, vape-free and tobacco-free, and nicotine-free. The appropriate covariance structure to be used will be assessed by the likelihood ratio test. The method of maximum likelihood will be employed to ensure participants with missing data are included in the model assuming the data is missing at random. However, if all follow-up data is missing then the participant will be excluded from the analyses. Intervention by visit interaction effects will be tested. Note the distribution of these continuous outcomes will be first assessed for normality and skewed data will be subjected to an appropriate transformation before analysis. Non-parametric analysis (Mann-Whitney tests) will be used for the continuous outcomes if data is skewed and cannot be transformed to be normally distributed.

The time to first lapse and relapse outcomes will be analysed using Kaplan-Meier curves, the log rank test, and Cox proportional hazards regression analysis. In these analyses the event is lapse/relapse and duration will be calculated as the number of days since EOT to date of first lapse/relapse during follow-up. Participants that have withdrawn will be censored on the last available visit, and participants that have not lapsed/relapsed by 6 months will be censored on the 6 month visit date.

8.7. Serious adverse events

All serious adverse event (SAE) data will be reported and coded to MedDRA classification system. All safety data will be summarized in the form of frequency distributions, descriptive statistics, and tabulations. This includes all SAE's, for the duration of the study.

SAE counts by number of events and people will be summarised. Separate tables will be given for general MedDRA categories, and for the detailed MedDRA codes. SAE counts by categories collected in Form X (type, relationship to study treatment and seriousness) will be summarised and separate table will also be given for the incidence rate ratios comparing the two treatment arms. Line listings will also be produced in order to examine all serious adverse events and multiple adverse events for a participant on the same date.

Additional adverse event analysis related to the CONSORT harms extension will be conducted where possible.

8.8. Cost-effectiveness analyses

The trial will include an incremental cost-effectiveness analysis, where resource utilisation is compared with health utility gain, across the two study arms. Following PHARMAC recommended methods for a cost-utility analysis, incremental QALYs per $1 million of total budget will be estimated by conducting a trial-based health economic evaluation. Resource utilisation is measured in terms of 2025 dollar costs. Health utility is estimated in terms of health-related quality of life (HRQoL) as per EQ-5D-5L, with application of a published New Zealand value set. Health resource use events captured for each individual participant will be valued using unit costs based on published New Zealand data (where available), and where they

are unavailable, published international data (subject to assessment of its applicability to the New Zealand context) or local estimates. EQ-5D scores assessed at different points in time will be transformed into QALYs by integration of the area under the curve. Costs and benefits will be discounted at a rate of 3.5% per annum. Rates of 0% and 5% will be used in sensitivity analyses. Both observed costs and QALYs will be subject to robust regression analysis to account for effects of baseline characteristics as well as the impact of missing data. Cost effectiveness will be estimated from both a consumer and a health sector perspective. Probabilistic sensitivity analysis will quantify uncertainty in the results. Subgroup analyses will explore the heterogeneity of cost-effectiveness across pre-specified groups: age, gender, former/never smokers, deprivation, and ethnicity. Where possible, equity-informative cost-effectiveness analysis will consider who benefits and who bears the cost.

9. DATA SAFETY AND MONITORING COMMITTEE

An internal Data safety monitoring committee (DSMC) will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMC will provide recommendations about stopping or continuing the trial. The DSMC will meet every 6 months. The first meeting will take place before the trial to consider the DSMC charter, SAP and other related documents. Closed reports will be provided to the DSMC by the study statistician.

APPENDIX I: LIST OF TABLE TEMPLATES

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- Table 1a. Participant accountability
- Table 1b. Baseline variables

Section 2. Descriptive summary of follow-up data
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Section 3. Analysis
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- Table 4a. Serious adverse event counts
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