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Cytisine versus varenicline for smoking cessation for Māori (the indigenous people of New Zealand) and their extended family: protocol for a randomized non-inferiority trial

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ABSTRACT

Background and aims Cytisine, a nicotinic acetylcholine receptor partial agonist (like varenicline) found in some plants, is a low-cost, effective smoking cessation medication that may appeal to Māori [the indigenous people of New Zealand (NZ)]. The RAUORA trial aims to determine the effectiveness, safety and cost-effectiveness of cytisine (Tabex®) versus varenicline (Champix®) for smoking cessation in Māori and the *whānau* (extended family) of Māori. **Design** Pragmatic, community-based, open-label randomized non-inferiority trial. **Setting** Lakes District Health Board region, NZ. **Participants** Daily smokers (n = 2140) who self-identify as Māori or *whānau* of Māori, and are: aged ≥ 18 years, motivated to quit smoking in the next 2 weeks, eligible for subsidized varenicline, able to provide verbal consent and have daily access to a mobile phone/internet. Recruitment uses multi-media advertising. **Intervention and comparator** Participants are randomized (1 : 1 ratio) to receive a prescription for 12 weeks of cytisine tablets [following the manufacturer's dosing regimen for 25 days, then one 1.5-mg tablet every 6 hours (two per day) until 12 weeks] or varenicline tablets (following the manufacturer's dosing regimen). Both groups receive brief stop-smoking advice from the prescribing doctor and withdrawal-orientated behavioural support via community-based stop-smoking counselling services (frequency, duration and mode of delivery tailored for participants) or a research assistant (six weekly 10–15-minute calls). Participants are advised to reduce their smoking over the first 4 days of treatment, with day 5 as their designated quit-date. **Measurements** The primary outcome is carbon monoxide-verified continuous abstinence at 6 months post-quit date. Secondary outcomes at 1, 3, 6 and 12 months post-quit date include: self-reported continuous abstinence, 7-day point prevalence abstinence, cigarettes per day, time to (re)lapse, adverse events, treatment adherence/compliance, treatment acceptability, nicotine withdrawal/urge to smoke and health-care utilization/health-related quality of life. **Comments** This trial compares cytisine and varenicline when used by the indigenous people of NZ and their extended family for smoking cessation.

Keywords Cytisine, effectiveness, indigenous, non-inferiority, randomized, safety trial, varenicline.

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INTRODUCTION

New Zealand (NZ) has a smoke-free 2025 goal (i.e. < 5% of adults smoking by 2025). To achieve this goal, net smoking cessation rates need to increase substantially, particularly for Māori [indigenous New Zealanders who, in 2016, comprised 14% of the NZ population [1]], who have a high prevalence of daily smoking (33%) compared with the general population (14%) [2]. Consequently, Māori have high rates of smoking-related disease, contributing to the 7–8-year life-expectancy gap between Māori and non-Māori in NZ [3,4].

Standard smoking cessation treatment in NZ combines behavioural support (BS) with pharmacotherapy (combination nicotine replacement therapy (NRT), bupropion or varenicline) [5]. Varenicline, a nicotinic acetylcholine receptor (nAChR) partial agonist, doubles the odds of quitting, compared with placebo [6]. However, varenicline is the most expensive smoking cessation medication (US $474–501 for a full 12-week course) [7]. In NZ, varenicline is available on prescription and is fully subsidized by the Pharmaceutical Management Agency of NZ (PHARMAC) under 'special authority' (an approval issued by the Ministry of Health, on application by a medical practitioner).

Cytisine is an alkaloid found in several plant species, including the NZ kōwhai tree (*Sophora tetraptera* J.F.Mill.) [8,9]. Like varenicline, cytisine is structurally similar to nicotine and acts as a partial agonist at nAChR [10,11]. Cytisine is taken orally (1.5 mg cytisine/tablet) for 25 days, starting with one tablet every 2 hours on days 1–3 (9 mg/day), tapering to one tablet every 6 hours on days 21–25 (3 mg/day). Users are advised to reduce the number of cigarettes smoked during the first 4 days of treatment, and quit on the fifth day. The drug has a half-life of 4.8 hours [12], compared with 17 hours for varenicline [13]. Trial evidence indicates that cytisine is superior to a placebo [6,14–16] and NRT [17] for smoking cessation, with adverse effects typically mild and self-limiting [6,14–17]. Effect sizes observed in a cytisine versus NRT trial [17] were similar to those in a trial comparing varenicline to NRT [18]. This finding, coupled with the current large market price difference between cytisine and varenicline [7], the low cost per quality-adjusted life-years (QALY) for cytisine [19] and recent economic evaluations [20,21] suggests that the two medications should be compared using a non-inferiority trial design. However, varenicline comes off-patent in May 2020; if cytisine becomes marketed more widely, the presence of an in-class competitor may exert a downward pressure on the price of both medicines. Cytisine's occurrence as a 'natural' product could also increase its appeal to Māori and other indigenous people, smokers in countries where the use of herbal medicines is widespread, and to those who do not wish to use other cessation medication to quit smoking.

We designed a pragmatic, community-based, randomized, non-inferiority trial (named RAUORA—a Māori word meaning 'to rescue') to evaluate the effectiveness, safety and cost-effectiveness of cytisine versus varenicline for smoking cessation. We hypothesize that 12 weeks' treatment with cytisine plus BS will be at least as effective as 12 weeks' treatment with varenicline plus BS at increasing quit rates at 6 months post quit-date. A similar non-inferiority trial, comparing 25 days' treatment with cytisine plus BS against 12 weeks' treatment with varenicline plus BS, is recruiting in Australia [22].

METHODS

Study population

The population of focus is NZ Māori and their *whānau* who smoke daily and reside in the Lakes District Health Board (DHB) region of NZ. *Whānau* of Māori means extended family [23], and includes people who are not themselves Māori by *whakapapa* (genealogy), but who live in a Māori *whānau* (e.g. in a household by marriage). In the Lakes DHB region of NZ (population 105 170 in 2016/17) 35.2% of the population are Māori [24]. The region has a higher proportion of smokers (18%) and Māori smokers (37%) compared with national averages (14 and 33%, respectively) [2].

Eligibility criteria

Participants are eligible if they self-identify as Māori or *whānau* of Māori, smoke daily and are motivated to quit within the next 2 weeks are aged ≥ 18 years, can provide verbal consent, and are eligible for subsidized varenicline under special authority (i.e. they have tried, but failed, to quit on at least two separate occasions using NRT, with at least one of these attempts involving a comprehensive cessation programme; or have tried previously to quit using bupropion or nortriptyline; and have not used funded varenicline in the last 12 months [25]). Participants must also have daily access to a mobile phone with text capability and/or e-mail, and access to the internet via computer and/or smartphone. Only one person per household can be enrolled into the study.

Exclusion criteria include pregnant and/or breast-feeding women, people enrolled in another smoking cessation programme/study, current users of NRT, bupropion, clonidine, nortriptyline, varenicline or e-cigarettes (with or without nicotine), people who have used varenicline or cytisine in the last 12 months and people with known hypersensitivity to the study medications. Additional self-reported exclusion criteria include: moderate/severe renal impairment; treatment for active/latent tuberculosis; a heart attack, stroke or severe angina within the last 2 weeks; uncontrolled high blood pressure (> 150 mmHg systolic, > 100 mmHg diastolic); and/or a history of seizures. These latter exclusions were requested by the approving ethics committee based on precautions listed in the cytisine product insert (Tabex®, manufactured by SoPharma, Bulgaria; supplied for the trial by Achieve Life Sciences) and animal studies [26,27].

Recruitment

Recruitment is through community-based advertising and promotion by community-based smoking cessation services and health professionals. Advertisements direct potential participants to register via the study website

and/or to call/text a researcher directly. Potential participants are telephoned by a research assistant, provided with further trial information and assessed for eligibility. Verbal consent is obtained from eligible and interested participants and baseline data are collected. Potential participants who are ineligible are provided with brief cessation support by the research assistant and referred to the national Quitline, the regional community-based cessation provider, and/or their general practitioner [GP]) [5].

Randomization: allocation concealment and sequence generation

The computer-generated randomization sequence is prepared by the study statistician in a 1 : 1 ratio using block randomization with varying block sizes. After baseline data are recorded, the research assistant advises the participant to await a telephone call from the study doctor regarding their treatment allocation. Prior to randomization, the study doctor reviews each participant's baseline data (including any potential contraindications to the study medicines), verifies that the participant is eligible for varenicline via the special authority process and (if required) contacts the participant's usual GP for clarification of any medical concerns. The study doctor randomizes eligible participants by computer while on the phone to them, then writes a prescription for the allocated medication.

Blinding

The trial is open-label. All authors (except T.K. and V.P.) are blinded to treatment allocation until after data lock and analysis; however, four authors are unblinded when reviewing serious adverse events (SAEs). The two medications look different and have different dosing regimens, therefore participants cannot be blinded. The research assistants are also unblinded, as questions related to the allocated medication are asked at follow-up.

Interventions

Participants are randomized to receive a prescription for a 12-week course of cytisine (Tabex®) or varenicline (Champix®). The study doctor advises participants to reduce their smoking during the first 4 days of treatment, so that they are not smoking at all by the fifth day (their designated quit date). Participants visit their preferred pharmacy to collect their allocated medicine. The prescription is uploaded by the study doctor to a secure website for the pharmacist to access. Participating pharmacies routinely stock and dispense varenicline, and are supplied with pre-packaged cytisine for the study. All study medication is free for participants. As part of the NZ special authority process pharmacies are required to dispense varenicline in three instalments in the first 8 weeks: (1) an initial 2-week starter pack plus two weeks' maintenance treatment; (2) 4 weeks' maintenance treatment; and (3) a further 4 weeks' maintenance treatment. To ensure comparability between the two arms, cytisine is dispensed in the same manner as varenicline.

Cytisine

Participants follow the dosing regimen as recommended by the manufacturer, namely:

- Days 1–3: one 1.5-mg tablet every 2 hours (maximum six daily)
- Days 4–12: one 1.5-mg tablet every 2.5 hours (maximum five daily)
- Days 13–16: one 1.5-mg tablet every 3 hours (maximum four daily)
- Days 17–20: one 1.5-mg tablet every 4–5 hours (maximum three daily)
- Days 21–25: one 1.5-mg tablet every 6 hours (maximum two daily)

To ensure comparability with the 12-week dosing regimen of varenicline, cytisine use continues past day 25 at a maintenance dose of one 1.5-mg tablet every 6 hours (two per day, equivalent to 3.0 mg/day) until 12 weeks. There is no prior trial evidence of extended cytisine treatment in smokers. The choice of maintenance dose was supported by: (1) a dosing schedule of 12 weeks appears safe based on unpublished pharmacology/toxicology studies in rats (3–6 months treatment) and dogs (6 months treatment) and (2) unpublished toxicology studies and pharmacokinetic repeat-dose modelling undertaken by Achieve Life Sciences (personal communication, February 2017). This evidence was presented to the NZ medicines regulatory authority, who approved the use of the extended dosing regimen.

Varenicline

Participants follow the dosing regimen as recommended by the manufacturer, namely:

- Days 1–3: one 0.5-mg tablet once daily
- Days 4–7: one 0.5-mg tablet twice daily
- Days 8–week 12: one 1.0-mg tablet twice daily

Behavioural support

Participants in both groups receive standard smoking cessation BS (motivational interviewing) available in NZ [5]. The study doctor delivers brief stop smoking advice immediately after randomization (reflecting the advice delivered by GPs and/or practice nurses [28]). Participants are also offered a choice of additional smoking cessation BS: either that offered within the community by Manaaki Ora Trust (Tipu Ora) or that offered by the trial research assistants. The first option reflects 'real-world' community-based

stop-smoking counselling services, i.e. the frequency, duration and mode of delivery of the support is tailored to the participant and can include individual support offered by telephone, text messaging and/or face-to-face, or group counselling. The trial research assistants provide 6 weeks of weekly BS telephone calls (each 10–15 minutes) post-randomization. Participants who are smoking at the end of the trial are offered further cessation support through a service of their choice.

Baseline assessments

- Demographics: date of birth; sex; education; *iwi* [tribe]; connectedness to *iwi* (measured on a five-point Likert scale, where one is 'not very connected' and five is 'very connected'); National Health Index number (a unique identifier allocated to all New Zealanders at birth, that enables data linkage with health records)
- Smoking history: age of initiation; cigarettes smoked per day; years as a regular smoker; previous unsuccessful quit attempts in past 12 months and method; type of cigarettes smoked per day (e.g. roll-your-own and/or factory-made)
- Other smoking-related information: cigarette dependence (measured by the Fagerström Test of Cigarette Dependence) [29,30]; belief in ability to quit smoking (measured on a five-point Likert scale, where one is 'very low' and five is 'very high'); whether they live with other smokers
- Alcohol use and abuse: measured using the Alcohol Use Disorders Identification Test (AUDIT-C) to identify people with hazardous drinking or active alcohol-use disorders [31]
- Signs and symptoms of nicotine withdrawal, and urge to smoke: measured using the Mood and Physical Symptoms Scale (MPSS) [32]
- Concomitant medication: information about types of medication currently used
- Health-related quality of life: measured using the NZ EQ-5D Tariff 2 [33]
- Healthcare utilization: measured using items recommended by PHARMAC [34], such as GP and nurse visits, hospital in- and out-patient visits, prescription medication used, pharmaceutical co-payments, ambulance transport, home and continuing care (if any)

Primary outcome

The primary outcome measure is 6-month continuous abstinence (Russell Standard) defined as self-report of smoking not more than 5 cigarettes from the quit date, supported by biochemical validation [35]. A research assistant will visit all participants who claim to be abstinent to obtain an expired air-carbon monoxide (CO) reading using a Bedfont Smokerlyzer (Bedfont Scientific Ltd, Maidstone, UK), with a reading of ≤ 9 parts per million (p.p.m.) signifying smoking abstinence [35].

Secondary outcomes

Secondary outcome measures (Table 1) are assessed at 1, 3 and 6 months post-quit date. Assessment at 1 month enables comparison with existing cytisine trials, as it represents the 'end of treatment' time-point for the standard 25-day cytisine dosing regimen.

- Seven-day point prevalence: the proportion of participants that has stopped smoking, defined as self-report of having smoked no cigarettes (not even a puff) in the past 7 days
- Continuous (lapse-free) abstinence: the proportion of participants that has stopped smoking, defined as self-report of smoking not more than 5 cigarettes from the quit date
- Time to first lapse: defined as time to first cigarette smoked from the quit date, even a single puff
- Time to first relapse: defined as time to smoking more than 5 cigarettes a day for three or more days in a row
- Cigarettes smoked per day, if the participant is smoking
- Signs and symptoms of nicotine withdrawal, and urge to smoke (3 months): measured using the MPSS [32]
- Adverse events (AE): the type, severity and outcome of self-reported AEs are collected at each follow-up call, with AEs coded using MedDRA. In addition, at the time of redeeming their prescription participants are provided with a log-in card to access a web-based AE diary (Table 2). Participants are asked to complete the diary daily for the first 4 weeks, then weekly until 14 weeks (i.e. for 2 weeks post-treatment). Automated texts and/or e-mails are sent daily (for the first 4 weeks) then weekly to prompt diary completion. Patient-initiated electronic AE reporting systems of this nature have previously been shown to be effective [36,37]. In addition, participants can report an AE at any time via: Facebook instant messaging, their GP, community pharmacist and/or the BS provider. Causality and the seriousness of any SAEs will be assessed using the WHO Causality Assessment Tool by three authors and the study doctor immediately after reporting, with disagreement resolved through discussion
- Acceptability (3 months): participants will be asked whether or not they would recommend their allocated treatment to another smoker, and what they liked or disliked about using the product
- Treatment adherence and compliance: script filled; self-reported pill counts; early stopping of allocated medication and reasons why
- Concomitant medication: other medications taken during the course of the study

Table 1 Details of follow-up.

Timing	*Call 1*			*Call 2*	*Call 3*	*Call 4*	*Call 5*
				1 month post-quit date	*3 months post-quit date*	*6 months post-quit date*	*12 months post-quit date*
Description	*Week 0 Eligibility screening (A), baseline data (B), randomization (R)*			*(+/− 5 days)*	*(+/− 7 days)*	*(+/− 7 days)*	*(+/− 7 days)*
Case report form	*A*	*B*	*R*	*Data collection C1*	*Data collection C3*	*Data collection C6*	*Data collection C12*
General data							
Eligibility criteria	X		X				
Verbal consent	X		X				
Age and sex		X					
Education		X					
Iwi and connectedness to *iwi*		X					
National Health Index number		X					
Current medication		X		X	X	X	X
Pregnancy	X			X	X	X	X
Smoking information							
Level of nicotine dependence		X					
Type of tobacco smoked		X					
Cigarettes smoked per day		X		X	X	X	X
Age started		X					
Years smoked		X					
Previous quit attempts/method		X					
Chances of quitting/effectiveness		X					
Smoking in last seven days				X	X	X	X
Any smoking since quit date				X	X	X	X
Live with other smokers		X					
Time to lapse				X	X	X	X
Time to relapse				X	X	X	X
Withdrawal signs/symptoms		X			X		
Carbon monoxide test						X	
Alcohol							
Alcohol use		X					
Cost-effectiveness data							
Healthcare utilization		X			X	X	X
Health-related quality of life		X			X	X	X
Follow-up details							
Quit date			X				
Contact details		X		X	X	X	X
Treatment allocation			X				
Intervention period (12 weeks)							
Behavioural support provided[a]			X	X			
Script redeemed				X	X		
Acceptability of treatment					X		
Use of treatment				X	X		
Other cessation support used				X	X	X	X
Adverse events				X	X	X	X

[a]Both groups receive brief stop-smoking advice from the prescribing doctor immediately after randomization, and withdrawal-orientated behavioural support from either community-based stop-smoking counselling services (the frequency, duration and mode of delivery is tailored for each participant) or the trial research assistants (six weekly 10–15-minute telephone calls post-quit date).

- Other cessation methods: e.g. NRT, bupropion, clonidine, nortriptyline, e-cigarettes, acupuncture, etc.
- Health-related quality of life (3 and 6 months): measured using the NZ EQ-5D Tariff 2 [33]
- Healthcare utilization: measured using items recommended by PHARMAC [34]

All women who are pregnant at follow-up are asked to discuss on-going smoking cessation support with their

Table 2 Schedule for adverse event data collection in first 14 weeks.

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Treatment period	→	→	→	→	→	→	→	→	→	→	→	→		
Quit Date (Day 5)	X													
Adverse event data *	Collected daily →							Collected weekly →						
Adverse event data also collected at scheduled follow-up calls (i.e. 1 month, 3 months, etc)				■								■		
Spontaneous reporting of adverse events	Available throughout the trial via Facebook instant messaging, participant's pharmacist, general practitioner													

*Web-based adverse event diary (a paper version of the diary will be provided if requested). Automated texts (which can be received even if the phone has no credit) and/or emails will be sent daily (for the first 4 weeks) then weekly as a prompt to complete the diary.

GP/lead maternity caregiver, and are withdrawn from the trial.

Twelve-month follow-up is not possible for all participants due to the 3-year funding time-frame. However, we estimate that two-thirds of the sample can be recruited in time to enable the following data to be collected at 12 months: 7-day point prevalence; continuous abstinence (biochemically verified); time to lapse/relapse; cigarettes smoked per day (if smoking); AEs.

Sample size

A sample size of 2140 (1070 in each group) confers 90% power at the one-sided significance level of 2.5% to detect a non-inferiority margin of 10% between the two groups [38]. The 6-month continuous abstinence quit rate in those who receive cytisine is assumed to be 22% [17]. A 6-month continuous abstinence quit rate of 28% was reported in a varenicline trial undertaken in secondary care [39]. However, we have chosen to be more conservative and have assumed a 25% quit rate, given our pragmatic design. The sample size accounts for a loss-to-follow-up at 6 months of 28%, based on a similar NZ non-inferiority cytisine trial [17].

Data management

All data are collected and managed using REDCap [40]. The study will be monitored after 10 participants have been randomized, at study close-out and twice during the course of the trial. An independent Data Safety and Monitoring Committee has been established, with clear terms of reference.

Statistical analysis

Statistical analyses will be undertaken by a statistician using SAS version 9.4 and R [41]. The analysis code will be written and finalized prior to datalock. No interim analyses are planned. Non-inferiority for the primary outcome will be evaluated by observing whether the lower bound of the two-sided 95% confidence interval (CI) for the risk difference in quit rates between the groups is above the non-inferiority limit of −10. The primary analyses will be carried out on an intention-to-treat basis where people with missing outcomes are assumed to be still smoking. In the case that non-inferiority is evident, assessment as to whether cytisine is superior to varenicline will be undertaken using the same approach, but compared to a zero difference. Non-inferiority studies should also be evaluated against a per protocol population, defined on the basis of compliance, protocol violations, and missing data [42,43]. Both sets of results will be considered when assessing the study objective. Medication compliance will be defined as having taken ≥ 80% of the required number of tablets 3 months post-quit.

Incidence rates, risk difference, relative risk and 95% CI will be calculated for all binary outcomes, groups will be compared using χ^2 tests, and multiple logistic regression will be conducted (if necessary) to adjust for imbalance in covariates. The number of cigarettes per day will be

assessed using multiple linear regression adjusted for baseline value. Symptoms of withdrawal (for abstainers) will be assessed using repeated-measures mixed models adjusted for baseline value. Time to lapse/relapse back to smoking will be analysed using Kaplan–Meier curves, log-rank test and Cox regression. AEs will be reported as the number of participants (and percentage) with any type of AE or SAE and incidence rate ratios. SAEs will be summarized according to the type of event (death, life threatening, hospitalization and other important medical event) and causality. Secondary analyses will be conducted with cessation rates corrected for any discordance between reported and verified cessation. Sensitivity analysis will be undertaken for the primary outcome replacing missing outcomes with multiple imputation if the level of missing data is deemed high (i.e. $> 20\%$), and also looking at different cut-offs for the CO measurement, given lack of consensus about the best reading to use. Pre-specified subgroup analyses will be undertaken for the primary outcome by age, sex, education, type of cigarettes smoked, level of nicotine dependence, baseline AUDIT-C score and level of BS received, using tests for heterogeneity.

Incremental QALYs per $1 million of total budget will be estimated by conducting a trial-based health economic evaluation [34]. Health resource use events captured for each participant will be valued using unit costs based on published NZ data (where available), and where they are unavailable, published international data (once its applicability to NZ's context is thoroughly assessed) or local estimates. The EQ-5D scores assessed at different points in time will be transformed into QALYs using the 'area under the curve' method [44]. Both observed costs and QALYs will be subject to robust regression analysis to account for baseline characteristics and missing data. A sensitivity analysis will assess the parameter uncertainty.

To estimate the costs and benefits of cytisine and varenicline beyond the trial period, a Markov state transition model (an adapted version of a BENESCO model [20], which has been used in several previous evaluations of this kind [45–47]) will be used. In this model, three states are assumed: current smokers, quitters and death. In the simulation, every year smokers and quitters may develop smoking attributable diseases. Utility decrements are assigned to both smoking attributable diseases and also to being a smoker or a quitter. Trial data will populate this model, as well as data from published sources applicable to NZ (as above). Both costs and outcomes will be discounted at a rate of 3.5% per annum for base case analysis. Findings will be presented as QALYs per $1 million total budget [34]. A sensitivity analysis will explore the extent of uncertainty in cost-effectiveness estimates [48], as well as the impact of a probable cost reduction for varenicline (once off-patent) on the cost-effectiveness of cytisine versus varenicline. In addition, the incremental cost-effectiveness ratios obtained by the method described by Leaviss *et al.* will be calculated [20].

Ethical considerations

With the exception of biochemical verification of quitting, trial participants are not seen and receive no reimbursement for their time (although trial medication is free). A two-step verbal consent process (documented on-line) is used. Ethics approval was obtained on 22 November 2016 from the Southern Health and Disability Ethics Committee (16/STH/147). Approval for use of an unregistered medicine (Tabex®) was obtained from the Standing Committee on Therapeutic Trials on 3 April 2017 (16/SCOTT/93).

Governance

In addition to steering and management committees, a Scientific and Dissemination Committee has been established to provide advice about the trial design, conduct and dissemination. Members have national and international experience in tobacco control, varenicline, cytisine, clinical safety, trial design and regulatory affairs. As a Māori-focused study, a *Kaitiaki* (Māori governance group) has been established to provide cultural advice and support, direction on appropriate ways to recruit and engage Māori into the trial and advice regarding data analysis, interpretation and dissemination of the trial findings. The *Kaitiaki* is supported by the NIHI Māori research advisory group, which is endorsed by the *Tumuaki* (Director) of the University of Auckland's Faculty of Medical and Health Sciences.

DISCUSSION

Recruitment started on 14 September 2017, with results expected to be available late 2019.

Clinical Trial Registration

Trial Registration number: NCT02957786

Declaration of interests

No authors have received financial support from any companies for the submitted work. N.W., J.B., V.P. and C. B. have previously received Tabex cytisine tablets from Dr Anthony Clarke and Richard Stewart for the conduct of a non-inferiority trial of cytisine versus NRT. N.W., C.B., V.P. and M.V. have received smoking cessation medication and matching placebo from Pfizer (under their investigator-initiated research programme, 2017) for the conduct of a smoking relapse prevention trial in patients with

chronic obstructive pulmonary disease. N.W. 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. C.B. has previously undertaken research funded by NicoNovum prior to its sale to RJ Reynolds and received benefits in kind (accommodation expenses) from a manufacturer of smoking cessation medications. J.B. was previously (1999–2002) a Lichtwer research fellow, has undertaken research funded by and has received benefits in kind and travel support from LichtwerPharma (a manufacturer of a herbal medicine used in smoking cessation). M.V. has previously (2010–13) undertaken research supported by an unrestricted grant from Pfizer.

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