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Complete List of Authors:	Gobarani, Rukshar; Monash University - Parkville Campus, Centre for Medicine Use and Safety Abramson, Michael; Monash University, Dept of Epidemiology and Preventive Medicine Bonevski, Billie; University of Newcastle, School of Medicine & Public Health Weeks, Gregory; Barwon Health Dooley, Michael; Monash University, Centre for Medicine Use and Safety; The Alfred, Pharmacy Department Smith, Brian; Bendigo Health - Bendigo Hospital Campus, Department of Clinical Epidemiology and Biostatistics Veale, Antony; The Queen Elizabeth Hospital, Department of Respiratory Medicine Webb, Ashley; Frankston Hospital, Department of Anaesthesia and Pain Management Kirsa, Sue; Monash Health, Pharmacy Thomas, Dennis; The University of Newcastle Hunter Medical Research Institute, Priority Research Centre for Healthy Lungs Miller, Alistair; Monash Health, General Medicine Unit and Monash Lung and Sleep Department Gasser, Rudi; Barwon Health, Department of General Medicine Paul, Eldho; Monash University, School of Public Health and Preventive Medicine; Alfred Health, Clinical Haematology Department Parkinson, Jacqueline; Monash Health, Pharmacy Meanger, Darshana; Frankston Hospital, Pharmacy Coward, Lisa; Frankston Hospital, Anaesthesia Kopsaftis, Zoe; The Queen Elizabeth Hospital, Respiratory Medicine and Clinical Practice Unit Rofe, Olivia; Eastern Health Foundation, Pharmacy Lee, Paula; Eastern Health Foundation, Pharmacy George, Johnson; Monash University, Centre for Medine Use and Safety
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The efficacy and safety of varenicline alone versus in combination with nicotine lozenges for smoking cessation among hospitalised smokers (VANISH): study protocol for a randomised, placebo-controlled trial

Authors:

Miss Rukshar K. Gobarani, BPharm (Hons), Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia; rukshar.gobarani@monash.edu

Prof Michael J. Abramson, PhD, FRACP, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; michael.abramson@monash.edu

Prof Billie Bonevski, PhD, School and Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia; billie.bonevski@newcastle.edu.au

Dr Gregory R. Weeks, PhD, Pharmacy Department, Barwon Health, Geelong, Victoria, Australia; greg@barwonhealth.org.au

Prof Michael J. Dooley, PhD, Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia; Pharmacy Department, The Alfred, Prahran, Victoria, Australia; M.Dooley@alfred.org.au

Prof Brian J. Smith, MBBS, FRACP**,** PhD, Dip Clin Epi and Biostats, Bendigo Hospital, Victoria, Australia; bsmith555@bigpond.com

Dr Antony Veale, MBBS, FRACP, Department of Respiratory Medicine, The Queen Elizabeth Hospital, Adelaide, Australia; antony.veale@sa.gov.au

Dr Ashley Webb, MBBS (Hons)**,** MPH, FANZCA Department of Anaesthesia and Pain Management, Peninsula Health, Frankston, Victoria, Australia; AWebb@phcn.vic.gov.au

A/Prof Sue Kirsa, Grad Dip Hosp Pharm, Pharmacy Department, Monash Health, Clayton, Victoria, Australia; Sue.Kirsa@monash.edu

Dr Dennis Thomas, PhD, Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, New South Wales, Australia; dennis.thomas@newcastle.edu.au

Dr Alistair Miller, MBBS, General Medicine Unit and Monash Lung and Sleep Department, Monash Health, Clayton, Victoria, Australia; alistair.miller@monashhealth.org

Dr Rudi Gasser, MBBS, Department of General Medicine, Barwon Health, Geelong, Victoria, Australia; rudig@barwonhealth.org.au

Dr Eldho Paul, PhD, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; Clinical Haematology Department, The Alfred, Melbourne, Victoria, Australia; eldho.paul@monash.edu

Ms Jacqueline Parkinson, MPharm, Pharmacy Department, Monash Health, Clayton, Victoria, Australia; Jacqueline.Parkinson@monashhealth.org

Miss Darshana Meanger, BPharm, Grad Cert Pharm Prac, Pharmacy Department, Peninsula Health, Frankston, Victoria, Australia; DMeanger@phcn.vic.gov.au

Ms Lisa Coward, EEN, Department of Anaesthesia, Peninsula Health, Frankston, Victoria, Australia; LCoward@phcn.vic.gov.au

Dr Zoe Kopsaftis, PhD, BHSc (Hons), Respiratory Medicine and Clinical Practice Unit, The Queen Elizabeth Hospital, Adelaide, South Australia, Australia; Zoe.Kopsaftis@sa.gov.au

Ms Olivia Rofe, BPharm, MPharm (Clin), Prof Cert Health Syst Management, Pharmacy Department, Eastern Health, Melbourne, Victoria, Australia; Olivia.Rofe@easternhealth.org.au

Ms Paula Lee, BPharm, Grad Dip Clin Res, Pharmacy Department, Eastern Health, Box Hill, Victoria, Australia; Paula.Lee@easternhealth.org.au

Dr Johnson George, PhD, Centre for Medicine Use and Safety, Parkville, Victoria, Australia; johnson.george@monash.edu

ABSTRACT

Introduction: Smoking is a leading cause of premature deaths globally. The health benefits of smoking cessation are many. However, majority of quit attempts are unsuccessful. One way to potentially improve success rates is to evaluate new combinations of existing smoking cessation therapies that may work synergistically to decrease the intensity of withdrawal symptoms and cravings.

Aims: To evaluate the feasibility, efficacy and safety of the combination of varenicline and nicotine replacement therapy (NRT) lozenges versus varenicline alone in assisting hospitalised smokers to quit.

Methods and analysis: This is a multi-centre, randomised, placebo-controlled trial. Adults with a history of smoking ≥10 cigarettes per day on average in the four weeks prior to their hospitalisation will be recruited. Participants will be randomly assigned to either the intervention group and will receive varenicline and NRT lozenges, or the control group and will receive varenicline and placebo lozenges. In addition to this, all participants will be actively referred to behavioural support from telephone Quitline. Participants are followed up at 1 and 3 weeks and 3, 6 and 12 months from the start of treatment. The primary outcome is carbon monoxide (CO) validated continuous abstinence from 2 weeks to 6 months after treatment initiation. Secondary outcomes include self-reported and biochemically validated continuous and point prevalence abstinence at 3, 6 and 12 months, self-reported adverse events, withdrawal symptoms and cravings, adherence to treatment, Quitline sessions attended etc. According to the Russell standard, all randomised participants will be accounted for in the primary intention-to-treat analysis.

Ethics and dissemination: The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, the National Health and Medical Research Council

(NHMRC) National Statement on Ethical Conduct in Human Research (updated 2015) and the Australian Code for the Responsible Conduct of Research (2018). Approval will be sought from the Human Ethics Committees of all the participating hospitals and the University. Written informed consent will be obtained from each participant at the time of recruitment.

Trial registration: Australia New Zealand Clinical Trials Registry: ACTRN12618001792213

Strengths and limitations of this study:

- This is the first multi-centre, randomised, placebo-controlled trial to evaluate the efficacy and safety of a combination of varenicline and an immediate-release form of NRT.
- This is also the first pragmatic trial exploring the effectiveness of this combination treatment in achieving long-term abstinence rates among inpatients in Australian hospitals.
- The multi-centre pragmatic design of the trial will ensure that the study sample is representative of the inpatient smokers who are admitted to Australian public hospitals allowing greater generalizability of study findings
- Biochemical verification of abstinence used in this trial will enable us to make accurate inferences regarding the effectiveness of the intervention.

BACKGROUND

Tobacco smoking is one of the leading causes of preventable morbidity and mortality around the world. Representing a key risk factor for deaths due to ischaemic heart disease, stroke and cancer, tobacco smoking kills approximately six million people globally each year (1). Holding the potential to damage nearly every organ system in the human body, tobacco smoking accounts for 7.8% of the total burden of disease in Australia (1, 2). Despite this, 14% of adults aged 18 years and over smoked daily in 2017-2018 (3).

Various therapeutic agents are currently available to assist in quitting smoking. A substantial body of research has demonstrated the effectiveness of such therapies in increasing abstinence rates (4). Of these, varenicline is the most effective single agent for abstinence outcomes. Available as a prescription only medicine in Australia, varenicline at the standard dose more than doubles the chances of quitting compared with placebo (pooled RR for continuous or sustained abstinence at six months or longer 2.24; 95% CI 2.06 to 2.43) (5). It has a dual mechanism of action and exerts its effects by acting as a partial agonist at the α4β2 nicotinic receptors in the brain (6). This reduces the drop in the mesolimbic dopaminergic levels that occurs during smoking cessation, relieving withdrawal symptoms (6). Varenicline also antagonises the activity of nicotine on its receptors which prevents the release of neurotransmitters such as dopamine and in doing so reduces feelings of pleasure experienced from a smoking relapse (6).

Nicotine replacement therapy (NRT) is another first line treatment for those seeking pharmacological help to quitting smoking (4). NRT replaces some of the nicotine in the blood that was previously derived from cigarettes, without the presence of the thousands of other chemicals that are also produced during tobacco combustion which are largely responsible for

causing tobacco-related illnesses (7, 8). In this manner, NRT decreases the intensity of withdrawal symptoms and cigarette cravings (7, 8).

In many countries, NRT is available over-the-counter in acute release formulations such as gums, lozenges, inhalers, mouth sprays and sublingual tablets and in slow release forms such as transdermal patches. Transdermal patches release nicotine slowly over a prolonged period of time (24 or 16 hour patches available) whereas, acute release forms of NRT provide a faster release of nicotine in the blood (7). Acute-dosing products allow the user to titrate both the amount and timing of their doses (7). Therefore, these forms of NRT can be used as "rescue-medication" by smokers to alleviate cigarette cravings (7).

NRTs are more effective than placebo in achieving long-term smoking abstinence (RR of abstinence for any form of NRT relative to control 1.55; 95% CI 1.49 to 1.61) (9). Various forms of NRT perform similarly against each other [pooled RRs of 1.64 for nicotine patch (95% CI 1.53 to 1.75); 1.49 for nicotine gum (95% CI 1.40 to 1.60) and 1.52 for oral tablets/lozenges (95% CI 1.32 to 1.74) relative to control], and evidence suggests that the use of two forms of NRT; a slow release formulation with an acute release formulation (i.e. combination NRT) is more effective than using a single form of NRT (9, 10).

Research to date suggests that varenicline (as monotherapy) and combination NRT are the most effective smoking cessation therapies that are currently available to assist in achieving abstinence (4). Even these, however, result in only modest increases in abstinence rates of approximately 30-40% at 6 months compared with placebo (11-15). A substantial amount of research is thus focused on evaluating new treatment options and approaches for smoking cessation to further increase abstinence rates (11).

In attempts to improve smoking cessation rates, new combinations of existing smoking cessation therapies have been evaluated (16-18). Current research suggests that varenicline may not fully saturate the nicotinic acetylcholine receptors in the brain (19). This in turn leads to only a partial attenuation of nicotine cravings (20). It has been postulated that adding NRT to varenicline treatment may therefore increase receptor saturation, which in turn may decrease cigarette cravings more completely (19, 20).

In response to this, studies have evaluated the effectiveness of the combination of varenicline and NRT patches versus varenicline monotherapy on smoking cessation rates, although findings have been equivocal (20, 21). A systematic review and meta-analysis of three randomised controlled trials demonstrated that the combination of varenicline and NRT patches was associated with significantly higher rates of abstinence versus varenicline alone at the end of treatment i.e. at 12 weeks (OR 1.50; 95% CI 1.14 to 1.97) and at 6 months (OR 1.62; 95% CI 1.18 to 2.23) (22). This association, however, did not exist when the largest of the three trials, which also used a pre-quit nicotine patch, was excluded from the analysis (22).

No studies to date have evaluated the effectiveness of the combination of varenicline and acute release forms of NRT which have proven to be just as effective as NRT patches in assisting smokers to quit (9). Secondly, steady-state plasma varenicline concentrations are achieved after approximately four days of continued treatment (19). During this time, patients may experience significant discomfort from withdrawal symptoms and often continue to smoke for several weeks after initiating varenicline therapy (19). Furthermore, a study reported that while varenicline reduces both tonic and cue-induced cigarette cravings, it does not attenuate cue-induced cravings after stress induction compared to placebo (23). In such situations, the use of an *ad lib* NRT product in combination with varenicline would thus enable patients to better

manage their withdrawal symptoms and cravings particularly to prevent stress and cue-related reinstatement of smoking (19, 23).

Smoking inside public hospitals and within 4 meters of the entrances to all public hospitals is prohibited in Australia (24). This restriction provides a window of opportunity for the implementation of smoking cessation interventions as inpatient smokers are placed away from their usual environmental triggers of smoking (25). During this time of increased vulnerability regarding their health, patients may be more motivated to quit and may also be more receptive to smoking cessation interventions and a change in behaviour particularly if they are presenting with conditions that may be caused or exacerbated by smoking (26-30).

Furthermore, hospitalised inpatients generally smoke a greater number of cigarettes per day than the general population and have a higher level of nicotine dependence (1, 31). Varenicline is a smoking cessation agent that is targeted towards moderate to heavy smokers (32-34). Therefore, this group of patients provide an ideal study population for evaluating the efficacy and safety of the combination of varenicline and nicotine lozenges for smoking cessation. In addition to this, an inpatient setting allows the trial medications to be commenced and administered under clinical supervision of hospital staff. This would ensure that participants have immediate access to a healthcare professional for medication education or management of an adverse drug event due to any trial medication. This study, therefore, aims to evaluate the effectiveness and safety of the combination of varenicline and NRT lozenges versus varenicline monotherapy in assisting hospitalised smokers in quitting.

Objectives

The primary objective of the study is to compare biochemically-verified continuous abstinence at 6 months in hospitalised smokers treated using varenicline plus NRT lozenges with those treated with varenicline and placebo lozenges.

The secondary objectives of this study are to compare:

- CO verified continuous abstinence from 2 weeks to 12 months after treatment initiation for participants who self-report abstinence at the 12-month follow-up
- Self-reported 7-day point prevalence abstinence and continuous abstinence measured from 2 weeks to 3, 6 and 12 months after treatment initiation
- CO verified 7-day point prevalence abstinence from 2 weeks to 6 and 12 months after treatment initiation for participants who self-report abstinence at these follow-ups
- Self-reported treatment adherence and adverse events to the study medicines at all follow-ups as well as number of Quitline sessions attended after treatment initiation.

METHODS

Study design

A randomised, placebo-controlled, multi-centre, double blinded study

Setting and Participants

Participants will be recruited from the inpatient wards of five 'smoke-free' public hospitals in Australia. Participants will be screened for eligibility at baseline and written informed consent will be sought. Eligible participants will be randomised to either the intervention or control group and will be followed up for 12 months from treatment initiation.

Inclusion and Exclusion criteria

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Patients eligible for the trial are: adults ≥18 years, admitted to participating hospitals with a history of smoking ≥10 cigarettes per day on average in the four weeks prior to their hospital admission, interested in quitting smoking, willing to use pharmacotherapy, available for a 12 months follow-up post-treatment initiation and willing/capable to provide written informed consent.

Patients who do not meet all of the above inclusion criteria, those who have a terminal illness with an anticipated survival of <6 months, those who have an unstable cardiovascular status (recent myocardial infarction or stroke within the past 3 months) or those with a new diagnosis of a major psychiatric illness (e.g. psychosis) within the past 3 months will be excluded from the study. Patients unable to communicate in English and provide written consent will also be excluded given the potential need to regularly communicate with the investigators during the entire trial period, and the lack of funding for interpreters.

Further exclusion criteria for this study are: women who are pregnant, breastfeeding or planning to become pregnant in the next 6 months and patients who were already using smoking cessation medications or approaches at the time of their hospital admission (i.e. NRT, varenicline, bupropion, clonidine, nortriptyline, or electronic nicotine delivering systems). In addition to this, patients who are currently participating in other smoking cessation programs/studies, those who have completed ≥12 weeks course of varenicline in the 12 months prior to hospitalisation (these patients may have a higher nicotine dependence and may not respond well to sole varenicline therapy), those who have had intolerable/serious adverse events from the use of varenicline or NRTs in the past, and those who have contraindications for their use (including those using medications known to have major interactions with either varenicline or NRT) will be excluded from the study.

Participant recruitment

Eligible participants will be identified through active screening of hospital records by a trained Research Assistant (RA), a nurse or a pharmacist employed at each site. Ward staff including doctors, nurses, pharmacists and physiotherapists will be informed of the study and asked to refer all patients identified as current smokers to the RA. Flyers containing study information will be displayed in hospital wards to notify inpatients of the study. Flyers will contain the contact information of the RA at the site so that interested patients can discuss the study with them.

Once potential participants are identified, the RA in consultation with the treating medical team will assess each patient's eligibility for the study considering their current health status and any apparent contraindications for the use of varenicline or NRT. Details of this initial medical screening will be recorded by the RA. The RA will then approach eligible patients, describe the project to each potential participant, provide a plain language statement and answer any questions. If the patient is interested in participating, written informed consent will be sought before proceeding with the baseline interview.

Baseline data collection

Each participant will be assigned a study number and baseline data collected. Data gathered during the interview will include information on the participant's smoking habits, previous attempts at quitting and current willingness/confidence to quit. A detailed medical history (current medical conditions and medications) including the presence of any contraindications or precautions for the use of the study medicines (based on the Product Information Sheets) will be sought. Participants with any exclusion criterion will not be enrolled, and will be

referred to Quitline for smoking cessation support. Participants who do not meet any of the exclusion criteria, but who have a cautionary condition, will be referred to an in-house clinician for further assessment. The decision on whether to include such participants will be at the discretion of the treating medical team, the RA and the patient based on an evaluation of the potential risks and benefits from participation in the study.

The baseline interview will also involve an assessment of the presence of psychological distress using the Patient Health Questionnaire (PHQ-9). Once baseline data collection is completed, to ensure the safe ongoing delivery of healthcare services to participants, the RA will seek the participants' consent to contact their regular general practitioner (GP) and community pharmacist to inform them of their patient's participation in the study.

Randomisation: allocation concealment and sequence generation

Following the collection of baseline data, participants will be randomised to one of the study arms by a clinical trials pharmacist at each of the five hospitals using a computer-generated randomisation list. Randomisation is stratified by site and random permuted block sizes of two and four will be used. Sealed opaque envelopes will be used for the concealment of treatment allocation. Each site will be provided with 64 envelopes containing group allocation. The clinical trials pharmacist at each site will open the envelopes in a sequential manner when a participant is recruited to identify group allocation. Once a participant's group allocation has been noted along with the study ID, study medicines will be charted on the participant's medication chart by a clinician involved in the study. The pharmacist will then dispense the study medicines as stated in the envelope ([varenicline and NRT lozenges] or [varenicline and placebo lozenges]) and hand these to the RA along with the envelope. The RA will then give the medicines to the participant and provide detailed counselling. Participants will not be told

whether they are receiving NRT or placebo lozenges. During hospital stay, the nurse in-charge of the ward will be responsible for daily administration of the medicines to the participant according to standard hospital practice. Participants will be asked to notify a nurse when they wish to have a lozenge (NRT or placebo).

Study arms and medicines

NRT and placebo (mint) lozenges will be repackaged and labelled in sachets containing two 2mg lozenges. For the initial supply, participants will be provided with 12 weeks supply of varenicline and 100 sachets of the NRT/placebo lozenges. The number of lozenges used on average per day will be assessed at the 3-week follow-up. Participants who would like additional supplies of the lozenges can have them delivered to their home by post.

Participants will be advised to commence the trial medication(s) during their hospital stay. The smoke-free policies of Australian hospitals create an environment conducive for abstinence. Therefore, all participants will be asked to reduce their smoking over the first seven days of varenicline treatment and aim to quit completely within two weeks. Patients will be asked to stop smoking in line with the varenicline Product Information Sheet (35). The RA involved in recruitment will provide verbal counselling to the participants on the dosing regimen, common adverse effects of the study medicines, who to contact in the event of an emergency, their contact details and how to obtain renewed supplies of trial medications. Participants will also be given Consumer Medicines Information (CMI) sheets on the study medicines and a lozenge instruction sheet highlighting key information on the dosing regimen and common adverse effects.

All study medicines (varenicline and the lozenges) will be initially given for a duration of 12 weeks. An additional 12 weeks course of the study medicines (varenicline and the lozenges) will be provided to participants who have ceased smoking during the initial course of treatment and are undergoing concurrent counselling (e.g. Quitline) for smoking cessation. At week 11 of treatment, RAs will contact participants in both treatment arms via telephone. At this time-point, participants who self-report continuous abstinence (i.e. smoking no more than 5 cigarettes between week-2 and week-11 of treatment) will be offered an additional 12 weeks of treatment using the same study medications. Participants will also be asked about their use of the Quitline service since the start of the study. The decision to provide the additional course of treatment will be at the discretion of a clinician at the recruiting site based on the participant's nicotine dependence, adherence to treatment, any adverse effects they may have experienced during the initial course and their severity. Additional supplies of the trial medications will be delivered to the participant's home by post or pick-up will be arranged from the recruiting hospital.

Control arm

Participants randomised to the control group will receive varenicline plus placebo (mint) lozenges. Varenicline will be used at the standard dose as follows: 0.5mg once daily on days 1-3, 0.5mg twice daily on days 4-7 and 1mg twice daily from day 8 onwards for 11 weeks.

Intervention arm

Participants randomised to the intervention arm will receive varenicline plus NRT lozenges. Varenicline will be used at the standard dose as in the control arm.

NRT/Placebo lozenge dosing schedule (36)

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Lozenges will be used by participants only when there is an urge to smoke. Participants will be advised to use a lozenge (2mg) as required when they have an urge to smoke (up to every 1-2 hours initially) and not to use more than 15 lozenges in a day. Participants will also be advised on how to use the lozenges as per the points below:

1. Place one lozenge on the tongue and suck until the taste becomes strong
2. Park the lozenge between the gum and cheek
3. When the taste fades start sucking the lozenge again
4. Repeat this process until the lozenge completely dissolves (it takes about 30 minutes)

Quitline support and text messages

All participants (both intervention and control) will be encouraged to use behavioural support from Quitline as per Quitline standard protocols. However, using Quitline support is not a compulsory requirement for participation in the study.

A Quitline referral form will be completed on behalf of the participant by the RA and sent to Quitline following the baseline interview. Quitline staff will contact the participant in the first instance at a suitable time noted on the referral form. Quitline staff will make a total of four attempts to contact the participant. If a participant is unreachable, Quitline will notify the RA at the respective site. The RA will follow this up with the participant at the next scheduled follow-up (1 or 3 weeks).

Automated text messages will be sent to all participants by Quitline using their standard procedures i.e. once a week for the first month of treatment, then once every month. Text messages will reinforce the importance of adherence to the study medicines to increase abstinence and also contain emergency contact details for the participants. Participants who do

not have a mobile phone will be called (with their permission) on their home phone by the RA instead of sending text messages.

Concomitant treatment

Participants will be able to take any other medicines as required, except for smoking cessation medicines, after discussing with the prescriber of their involvement in the trial. Use of concomitant medicines will be assessed and recorded at each follow-up and verification of any potential interactions with the study medicines will be carried out. The use of other smoking cessation medicines including other forms of NRT (e.g. patches) will be strongly discouraged during the course of the study. If a participant uses other smoking cessation medicines during the study period, an appropriate record of this will be maintained. Data from such participants will still be included in the primary and secondary analyses, however sensitivity analysis will be performed after excluding them from the primary analysis.

Data Collection and follow-up

Baseline data will be collected at the time of recruitment. All participants will be followed up for a period of 12 months after treatment initiation. Five follow-up interviews will be conducted: at weeks one and three of treatment and at three, six and twelve months after the start of treatment. The first and second follow-ups will be done by the RA and will be conducted face-to-face for participants who are still inpatients, or via telephone for participants who have been discharged. Three-, six- and twelve- month follow-ups will be conducted via telephone by a RA, who is blinded to treatment allocation and who was not involved in participant recruitment. Participants unable to be contacted for follow-ups will be considered as "smokers" according to the Russell Standard (37).

General demographics including age, gender, ethnicity, highest level of education, employment status and possession of any concession card will be collected at baseline. Medical and medication history will be obtained from the patients' hospital notes. Smoking-related information such as current smoking status, age at smoking onset, environmental triggers to smoking and previous attempts at smoking cessation will also be gathered. In addition to this, the study will employ the following validated scales:

- ***Heaviness of Smoking Index (HSI):*** the two item scale measures nicotine dependence and considers time to the first cigarette of the day and the number of cigarettes smoked per day (38).
- ***Patient Health Questionnaire (PHQ-9):*** this nine-item scale will be used to measure and monitor symptoms of depression amongst participants. Each item will be scored on a four point scale ranging from 'not at all' to 'nearly every day'(39).
- ***Visual analogue scales*** to assess the participants' level of motivation and confidence to quit smoking: a 10-point numerical scale with one being 'very low' to 10 being 'very high' will be used for participants to self-report their motivation and confidence to quit smoking.
- ***Mood and physical symptoms scale (MPSS):*** This questionnaire assesses the severity of withdrawal symptoms and the strengths and frequencies of patients' urges to smoke. The MPSS involves 5-point ratings of depressed mood, irritability, restlessness, difficulty concentrating and hunger and 6-point ratings of strength of urges to smoke and time spent with urges (40).
- ***Tool for adherence behaviour screening (TABS):*** This is an 8-item tool that assesses both intentional and unintentional non-adherence, participants rate each adherence behaviour statement on a 5-point scale ranging from 'always' to 'never' (41).

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Blinding

Three-, six- and twelve- month follow-ups will be conducted by a RA blinded to treatment allocation. All possible measures will be taken to prevent participant disclosure of treatment allocation to the RA. Any accidental unblinding will be documented and reported.

Primary endpoints

The primary endpoint is biochemically verified continuous abstinence from 2 weeks to 6 months after treatment initiation. A 2-week period will be allowed on treatment commencement to match the recommended grace period in the varenicline Product Information Sheet (35). Participants who self-report continuous abstinence (i.e. self-report of having smoked no more than five cigarettes, including the use of non-combustible tobacco products and electronic cigarettes) over this period (i.e. weeks 2- 26) will be asked to perform a carbon monoxide (CO) breath test. CO levels will be measured by a trained RA blinded to treatment allocation, using a handheld piCO+ Smokerlyzer (Bedfont Scientific, Maidstone, Kent, UK) during a hospital or home visit. Participants with a CO level <10 ppm will be considered abstinent (18, 42). Sensitivity analysis will be performed using a lower CO cut-off of <5ppm (43).

Secondary endpoints

The secondary outcomes are:

1) Participant self-reported continuous abstinence from 2 weeks to three, six and twelve months after treatment initiation

2) CO verified continuous abstinence from 2 weeks to 12 months after treatment initiation for participants who self-report abstinence at this follow-up

2) Self-reports of withdrawal symptoms and cravings

3) Self-reports of adherence to varenicline treatment measured using the TABS

4) Self-reports of the number of lozenges consumed per day (NRT or placebo)

5) Change in psychological distress

6) Adverse events experienced from the study medicines

7) Number of Quitline sessions attended/received (self-reported and data transfer from Quitline)

8) Self-reported utilisation of other smoking cessation therapies and alternative products (e.g. electronic cigarettes)

9) Self-reported 7-day point prevalence abstinence (i.e. smoking not even a puff in the past 7 days on the day of follow-up) at 3, 6 and 12 months after treatment initiation

10) CO verified 7-day point prevalence abstinence at 6 and 12 months after treatment initiation for participants who self-report abstinence at these follow-ups

Withdrawal criteria

All participants are strongly encouraged to complete the study, however there may be situations where withdrawal from the study may be appropriate. Participants may withdraw from the study if one or more of the following occur:

- The participant experiences any serious adverse event (SAE) from the use of the study medicines. Prior to treatment discontinuation, input from the treating medical team and Data Safety and Monitoring Board (DSMB) will be sought in establishing the association between treatment exposure and adverse events. The DSMB will review all such cases and make the final judgement on causality.
- If a female participant becomes pregnant during the course of treatment
- If a participant's health status changes significantly and the study medications are no longer in the best interest of the participant

- The lead investigators or health professionals perceive, for any reason, that the study is no longer in the best interest of the participant
- A participant may be withdrawn from the study if he/she wants to do so. Participants are free to withdraw from the study at any time without providing any reason or being disadvantaged.

A participant wishing to withdraw from the study will be asked to complete a 'withdrawal form' for record purposes, but it is not mandatory. Once withdrawn from the study, the participant will not be contacted for further data collection, however the available data will be included in the intention-to-treat analysis. If withdrawal is the result of an adverse drug reaction, the participants will be followed until the adverse reaction resolves or when they return to clinically acceptable medical status.

Sample size

To show an absolute difference of 15% in continuous abstinence rate between study arms (estimate based on continuous abstinence rates in varenicline-NRT trials)(21) at the 5% level of significance with 80% power, we will need 160 subjects per arm. A total of 320 participants will be recruited from the five hospitals, i.e. 64 subjects from each hospital, 32 each in varenicline monotherapy and varenicline + NRT arms. The primary analysis will be by ITT and participants lost to follow-up will be regarded as smokers (37).

Data analysis

The distribution of data will be assessed and analysed using appropriate statistical tests. The baseline demographic and clinical characteristics will be summarised using counts and proportions, mean and standard deviation or median and interquartile range, according to data type and distribution.

As recommended by the Russell Standard, all randomised patients will be accounted for in the ITT analysis (37). Participants with missing outcomes at follow-up, or whose self-reported abstinence was not biochemically validated will be considered as smokers. Sensitivity analyses using multiple imputation methods will also be carried out. Deceased participants will be excluded from analyses. In a supportive analysis of the primary efficacy endpoint, an analysis will also be conducted on the per protocol set, which excludes patients with any major protocol deviations. Use of NRT after admission to the hospital will be captured and adjusted for in the analysis. The statistical analysis plan will be finalised to provide a detailed description of all the analyses prior to locking of the database.

Continuous abstinence at six and twelve months in each treatment arm will be estimated. Differences between arms and the corresponding 95% confidence interval will be determined. Primary analysis will be performed using a cut-off CO of <10ppm and additional sensitivity analysis will be conducted using a lower cut-off of <5ppm (43). Logistic regression models will be used to examine the efficacy of intervention on the primary outcome, after testing homogeneity between hospitals using a random effects meta-analysis. In the event of heterogeneity, generalised estimating equation models incorporating clustering by hospital will be fitted. The effect of intervention on continuous abstinence at 6 and at 12 months will be tested in pre-specified subgroups (per hospital, nicotine dependence, highly motivated versus moderately motivated smokers and men versus women) using models fitted for each subgroup containing main effects for intervention and subgroup and an interaction between them. Statistical significance will be set at a two-sided p value of 0.05.

All randomised participants who take at least one dose of the treatment medications will be included in the safety analysis. A chi-squared test or Fisher's exact test as appropriate will be used to compare the frequency of treatment withdrawal between the intervention and control groups. The number of participants discontinuing treatment prematurely for any reason will be summarised by treatment group and by reasons for discontinuation.

The incidence of all suspected adverse events will be summarised by treatment group under the following categories: type, severity, action taken and outcome. Adverse event reports detailing the relationship of all adverse events occurs in response to the study medication will also be prepared. Severity of adverse events will be reported using the Common Terminology Criteria for Adverse Events (CTCAE) grading scale (v5.0). The causality of the adverse events will be determined using the Naranjo algorithm (44).

Data safety and monitoring board (DSMB)

To ensure the safety of the study participants and protect the scientific integrity of the trial, a three-member independent DSMB together with a study statistician has been established. The DSMB will periodically review trial safety and outcome data and make recommendations regarding the continuation of the trial based on this information. All serious adverse events (SAEs) will be adjudicated by an end point evaluation committee, which reviews documentation related to the SAE and decides regarding its potential causal relationship with the study drug. Suspected SAEs are also reported as required to the ethics committee of the hospital which enrolled the participant, the human research ethics committee of Monash University, and to the study sponsor. Treatment will be discontinued if there are SAEs or safety concerns relating to the use of the study medicines. Any support necessary to those affected or concerned will be provided independent of the study.

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ETHICS AND DISSEMINATION

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2015) and the Australian Code for the Responsible Conduct of Research (2018). Approval has been obtained from the Human Ethics Committees of all the participating hospitals and the University. Written informed consent will be obtained from each participant at the time of recruitment.

Both varenicline and NRT have well established safety and efficacy when used appropriately. However, participant safety may still be a concern, especially in combination. Any potential concerns regarding eligibility will be discussed with the treating medical team. Participants in both arms will be closely monitored for any adverse effects.

Participants will receive their CO breath test result immediately after testing. After data analysis, a summary of findings will be sent to participants who requested this information. The research team will submit study findings to peer-reviewed journals. Any protocol changes will be updated on the ANZ Clinical Trials Registry.

PATIENT AND PUBLIC INVOLVEMENT

This research will be done without patient or public involvement. Patients and the public will not be invited to comment on the study design and will not be consulted to develop patient relevant outcomes, interpret the results or contribute to the writing or editing of study documents for readability or accuracy.

DISCUSSION

Abstinence rates are suboptimal despite the wide availability of various smoking cessation therapies (4). A significant number of quit attempts result in failure; despite this no new smoking cessation medication has been approved by the Food and Drugs Administration since varenicline in 2006 (11). Effective combinations of existing smoking cessation therapies are thus needed to further boost abstinence rates.

This is the first multi-centre, placebo-controlled, randomised controlled trial to evaluate the efficacy and safety of a combination of varenicline with acute release forms of NRT. This is also the first pragmatic trial to explore the effectiveness of this combination treatment in achieving long-term abstinence rates among inpatients in Australian hospitals. Varenicline has proven to be one of the most effective smoking cessation therapies, however current literature suggests that it may not completely attenuate nicotine cravings. This effect could be overcome by the addition of an acute release form of NRT (11, 20). If effective this combination treatment may help to further boost abstinence rates and the results of this trial could help guide future smoking cessation treatments and guidelines. Smoking is banned in the premises of all the participating hospitals. This smoke-free environment will help to promote smoking cessation in both the intervention and the control arms of the study.

Some strengths of the current study include the randomisation of participants to the intervention and control arms reducing selection bias and outcome assessment by staff blinded to treatment allocation. The multi-centre design of the trial will ensure that the study sample is representative of the inpatient smokers who are admitted to Australian public hospitals. It will also enable greater generalisability of the study findings. Furthermore, biochemical verification of abstinence used in this trial will enable us to make accurate inferences regarding the

effectiveness of the intervention. According to standard practices, public hospitals in Australia offer NRT to inpatient smokers on admission to help them to abide to the hospital's smoke-free policy. As a result, some participants may already be using NRT (e.g. patch) when they are recruited. This may affect the participant's initial response to the study medication and would be one of the potential limitations of this study. Use of NRT after admission to the hospital will be captured and adjusted for in analysis.

TRIAL STATUS

This trial is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12618001792213). Approval will be sought from the Human Research Ethics Committees of all the participating hospitals and Monash University.

AUTHORS' CONTRIBUTIONS

JG conceived the research idea and developed it with input from other chief investigators, MA, BB, GW, MD, BS, AW and SK and secured research funding. RG is a PhD scholar working on this project under the supervision of JG, MA and BB. All the investigators contributed to all phases of the study including study design, protocol development and finalisation of manuscript. All authors have reviewed this manuscript and have approved the final protocol.

FUNDING

This study is supported by the Global Research Awards for Nicotine Dependence 2017, an independently-reviewed competitive grants program supported by Pfizer.

COMPETING INTERESTS

Michael Abramson, Billie Bonevski and Johnson George have held investigator-initiated grants from Boehringer Ingelheim (BI) Pty Ltd for an unrelated project. Michael Abramson has also received assistance with conference attendance and conducted an unrelated consultancy for Sanofi. He has also received a speaker's fee from GSK. Johnson George has received honorarium from GSK and Pfizer for consultancy and educational grants for unrelated projects.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 & 25
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	10

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	19
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	17
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	

		(see Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11&12

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-22
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	23
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	22

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of	#28	Financial and other competing interests for principal	25

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	22
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

BMJ Open

The efficacy and safety of varenicline alone versus in combination with nicotine lozenges for smoking cessation among hospitalised smokers (VANISH): study protocol for a randomised, placebo-controlled trial

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Complete List of Authors:	Gobarani, Rukshar; Monash University - Parkville Campus, Centre for Medicine Use and Safety Abramson, Michael; Monash University, Dept of Epidemiology and Preventive Medicine Bonevski, Billie; University of Newcastle, School of Medicine & Public Health Weeks, Gregory; Barwon Health Dooley, Michael; Monash University, Centre for Medicine Use and Safety; The Alfred, Pharmacy Department Smith, Brian; Bendigo Health - Bendigo Hospital Campus, Department of Clinical Epidemiology and Biostatistics Veale, Antony; The Queen Elizabeth Hospital, Department of Respiratory Medicine Webb, Ashley; Frankston Hospital, Department of Anaesthesia and Pain Management Kirsa, Sue; Monash Health, Pharmacy Thomas, Dennis; The University of Newcastle Hunter Medical Research Institute, Priority Research Centre for Healthy Lungs Miller, Alistair; Royal Melbourne Hospital, Respiratory and Sleep Medicine Gasser, Rudi; Barwon Health, Department of General Medicine Paul, Eldho; Monash University, School of Public Health and Preventive Medicine; Alfred Health, Clinical Haematology Department Parkinson, Jacqueline; Monash Health, Pharmacy Meanger, Darshana; Frankston Hospital, Pharmacy Coward, Lisa; Frankston Hospital, Anaesthesia Kopsaftis, Zoe; The Queen Elizabeth Hospital, Respiratory Medicine and Clinical Practice Unit Rofe, Olivia; Eastern Health Foundation, Pharmacy Lee, Paula; Eastern Health Foundation, Pharmacy George, Johnson; Monash University, Centre for Medine Use and Safety
Primary Subject Heading:	Smoking and tobacco
Secondary Subject Heading:	Addiction, Public health, Smoking and tobacco
Keywords:	PUBLIC HEALTH, Clinical trials < THERAPEUTICS, PRIMARY CARE

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1

The efficacy and safety of varenicline alone versus in combination with nicotine lozenges for smoking cessation among hospitalised smokers (VANISH): study protocol for a randomised, placebo-controlled trial

Authors:

Miss Rukshar K. Gobarani, BPharm (Hons), Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia; rukshar.gobarani@monash.edu

Prof Michael J. Abramson, PhD, FRACP, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; michael.abramson@monash.edu

Prof Billie Bonevski, PhD, School and Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia; billie.bonevski@newcastle.edu.au

Dr Gregory R. Weeks, PhD, Pharmacy Department, Barwon Health, Geelong, Victoria, Australia; greg@barwonhealth.org.au

Prof Michael J. Dooley, PhD, Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia; Pharmacy Department, The Alfred, Prahran, Victoria, Australia; M.Dooley@alfred.org.au

Prof Brian J. Smith, MBBS, FRACP**,** PhD, Dip Clin Epi and Biostats, Bendigo Hospital, Victoria, Australia; bsmith555@bigpond.com

Dr Antony Veale, MBBS, FRACP, Department of Respiratory Medicine, The Queen Elizabeth Hospital, Adelaide, Australia; antony.veale@sa.gov.au

Dr Ashley Webb, MBBS (Hons)**,** MPH, FANZCA Department of Anaesthesia and Pain Management, Peninsula Health, Frankston, Victoria, Australia; AWebb@phcn.vic.gov.au

A/Prof Sue Kirsa, Grad Dip Hosp Pharm, Pharmacy Department, Monash Health, Clayton, Victoria, Australia; Sue.Kirsa@monash.edu

Dr Dennis Thomas, PhD, Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, New South Wales, Australia; dennis.thomas@newcastle.edu.au

Dr Alistair Miller, MBBS, Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Melbourne, Victoria, Australia; alistair.miller3@mh.org.au

Dr Rudi Gasser, MBBS, Department of General Medicine, Barwon Health, Geelong, Victoria, Australia; rudig@barwonhealth.org.au

Dr Eldho Paul, PhD, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; Clinical Haematology Department, The Alfred, Melbourne, Victoria, Australia; eldho.paul@monash.edu

Ms Jacqueline Parkinson, MPharm, Pharmacy Department, Monash Health, Clayton, Victoria, Australia; Jacqueline.Parkinson@monashhealth.org

Miss Darshana Meanger, BPharm, Grad Cert Pharm Prac, Pharmacy Department, Peninsula Health, Frankston, Victoria, Australia; DMeanger@phcn.vic.gov.au

Ms Lisa Coward, EEN, Department of Anaesthesia, Peninsula Health, Frankston, Victoria, Australia; LCoward@phcn.vic.gov.au

Dr Zoe Kopsaftis, PhD, BHSc (Hons), Respiratory Medicine and Clinical Practice Unit, The Queen Elizabeth Hospital, Adelaide, South Australia, Australia; Zoe.Kopsaftis@sa.gov.au

Ms Olivia Rofe, BPharm, MPharm (Clin), Prof Cert Health Syst Management, Pharmacy Department, Eastern Health, Melbourne, Victoria, Australia; Olivia.Rofe@easternhealth.org.au

Ms Paula Lee, BPharm, Grad Dip Clin Res, Pharmacy Department, Eastern Health, Box Hill, Victoria, Australia; Paula.Lee@easternhealth.org.au

Dr Johnson George ***(corresponding author)***, PhD, Centre for Medicine Use and Safety, Parkville, Victoria, Australia; johnson.george@monash.edu

ABSTRACT

Introduction: Smoking is a leading cause of premature deaths globally. The health benefits of smoking cessation are many. However, majority of quit attempts are unsuccessful. One way to potentially improve success rates is to evaluate new combinations of existing smoking cessation therapies that may work synergistically to decrease the intensity of withdrawal symptoms and cravings.

Aims: To evaluate the feasibility, efficacy and safety of the combination of varenicline and nicotine replacement therapy (NRT) lozenges versus varenicline alone in assisting hospitalised smokers to quit.

Methods and analysis: This is a multi-centre, randomised, placebo-controlled trial. Adults with a history of smoking ≥10 cigarettes per day on average in the four weeks prior to their hospitalisation will be recruited. Participants will be randomly assigned to either the intervention group and will receive varenicline and NRT lozenges, or the control group and will receive varenicline and placebo lozenges. In addition to this, all participants will be actively referred to behavioural support from telephone Quitline. Participants are followed up at 1 and 3 weeks and 3, 6 and 12 months from the start of treatment. The primary outcome is carbon monoxide (CO) validated continuous abstinence from 2 weeks to 6 months after treatment initiation. Secondary outcomes include self-reported and biochemically validated continuous and point prevalence abstinence at 3, 6 and 12 months, self-reported adverse events, withdrawal symptoms and cravings, adherence to treatment, Quitline sessions attended etc. According to the Russell standard, all randomised participants will be accounted for in the primary intention-to-treat analysis.

Ethics and dissemination: The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, the National Health and Medical Research Council

(NHMRC) National Statement on Ethical Conduct in Human Research (updated 2015) and the Australian Code for the Responsible Conduct of Research (2018). Approval will be sought from the Human Ethics Committees of all the participating hospitals and the University. Written informed consent will be obtained from each participant at the time of recruitment.

Trial registration: Australia New Zealand Clinical Trials Registry: ACTRN12618001792213

Strengths and limitations of this study:

- This is the first multi-centre, randomised, placebo-controlled trial to evaluate the efficacy and safety of a combination of varenicline and an immediate-release form of NRT.
- This is also the first pragmatic trial exploring the effectiveness of this combination treatment in achieving long-term abstinence rates among inpatients in Australian hospitals.
- The multi-centre pragmatic design of the trial will ensure that the study sample is representative of the inpatient smokers who are admitted to Australian public hospitals allowing greater generalizability of study findings
- Biochemical verification of abstinence used in this trial will enable us to make accurate inferences regarding the effectiveness of the intervention.

BACKGROUND

Tobacco smoking is one of the leading causes of preventable morbidity and mortality around the world. Representing a key risk factor for deaths due to ischaemic heart disease, stroke and cancer, tobacco smoking kills approximately six million people globally each year (1). Holding the potential to damage nearly every organ system in the human body, tobacco smoking accounts for 7.8% of the total burden of disease in Australia (1, 2). Despite this, 14% of adults aged 18 years and over smoked daily in 2017-2018 (3).

Various therapeutic agents are currently available to assist in quitting smoking. A substantial body of research has demonstrated the effectiveness of such therapies in increasing abstinence rates (4). Of these, varenicline is the most effective single agent for abstinence outcomes. Available as a prescription only medicine in Australia, varenicline at the standard dose more than doubles the chances of quitting compared with placebo (pooled RR for continuous or sustained abstinence at six months or longer 2.24; 95% CI 2.06 to 2.43) (5). It has a dual mechanism of action and exerts its effects by acting as a partial agonist at the α4β2 nicotinic receptors in the brain (6). This reduces the drop in the mesolimbic dopaminergic levels that occurs during smoking cessation, relieving withdrawal symptoms (6). Varenicline also antagonises the activity of nicotine on its receptors which prevents the release of neurotransmitters such as dopamine and in doing so reduces feelings of pleasure experienced from a smoking relapse (6).

Nicotine replacement therapy (NRT) is another first line treatment for those seeking pharmacological help to quitting smoking (4). NRT replaces some of the nicotine in the blood that was previously derived from cigarettes, without the presence of the thousands of other chemicals that are also produced during tobacco combustion which are largely responsible for

causing tobacco-related illnesses (7, 8). In this manner, NRT decreases the intensity of withdrawal symptoms and cigarette cravings (7, 8).

In many countries, NRT is available over-the-counter in acute release formulations such as gums, lozenges, inhalers, mouth sprays and sublingual tablets and in slow release forms such as transdermal patches. Transdermal patches release nicotine slowly over a prolonged period of time (24 or 16 hour patches available) whereas, acute release forms of NRT provide a faster release of nicotine in the blood (7). Acute-dosing products allow the user to titrate both the amount and timing of their doses (7). Therefore, these forms of NRT can be used as "rescue-medication" by smokers to alleviate cigarette cravings (7).

NRTs are more effective than placebo in achieving long-term smoking abstinence (RR of abstinence for any form of NRT relative to control 1.55; 95% CI 1.49 to 1.61) (9). Various forms of NRT perform similarly against each other [pooled RRs of 1.64 for nicotine patch (95% CI 1.53 to 1.75); 1.49 for nicotine gum (95% CI 1.40 to 1.60) and 1.52 for oral tablets/lozenges (95% CI 1.32 to 1.74) relative to control], and evidence suggests that the use of two forms of NRT; a slow release formulation with an acute release formulation (i.e. combination NRT) is more effective than using a single form of NRT (9, 10).

Research to date suggests that varenicline (as monotherapy) and combination NRT are the most effective smoking cessation therapies that are currently available to assist in achieving abstinence (4). Even these, however, result in only modest increases in abstinence rates of approximately 30-40% at 6 months compared with placebo (11-15). A substantial amount of research is thus focused on evaluating new treatment options and approaches for smoking cessation to further increase abstinence rates (11).

In attempts to improve smoking cessation rates, new combinations of existing smoking cessation therapies have been evaluated (16-18). Current research suggests that varenicline may not fully saturate the nicotinic acetylcholine receptors in the brain (19). This in turn leads to only a partial attenuation of nicotine cravings (20). It has been postulated that adding NRT to varenicline treatment may therefore increase receptor saturation, which in turn may decrease cigarette cravings more completely (19, 20).

In response to this, studies have evaluated the effectiveness of the combination of varenicline and NRT patches versus varenicline monotherapy on smoking cessation rates, although findings have been equivocal (20, 21). A systematic review and meta-analysis of three randomised controlled trials demonstrated that the combination of varenicline and NRT patches was associated with significantly higher rates of abstinence versus varenicline alone at the end of treatment i.e. at 12 weeks (OR 1.50; 95% CI 1.14 to 1.97) and at 6 months (OR 1.62; 95% CI 1.18 to 2.23) (22). This association, however, did not exist when the largest of the three trials, which also used a pre-quit nicotine patch, was excluded from the analysis (22).

No studies to date have evaluated the effectiveness of the combination of varenicline and acute release forms of NRT which have proven to be just as effective as NRT patches in assisting smokers to quit (9). Secondly, steady-state plasma varenicline concentrations are achieved after approximately four days of continued treatment (19). During this time, patients may experience significant discomfort from withdrawal symptoms and often continue to smoke for several weeks after initiating varenicline therapy (19). Furthermore, a study reported that while varenicline reduces both tonic and cue-induced cigarette cravings, it does not attenuate cue-induced cravings after stress induction compared to placebo (23). In such situations, the use of an *ad lib* NRT product in combination with varenicline would thus enable patients to better

manage their withdrawal symptoms and cravings particularly to prevent stress and cue-related reinstatement of smoking (19, 23).

Smoking inside public hospitals and within 4 meters of the entrances to all public hospitals is prohibited in Australia (24). This restriction provides a window of opportunity for the implementation of smoking cessation interventions as inpatient smokers are placed away from their usual environmental triggers of smoking (25). During this time of increased vulnerability regarding their health, patients may be more motivated to quit and may also be more receptive to smoking cessation interventions and a change in behaviour particularly if they are presenting with conditions that may be caused or exacerbated by smoking (26-30).

Furthermore, hospitalised inpatients generally smoke a greater number of cigarettes per day than the general population and have a higher level of nicotine dependence (1, 31). Varenicline is a smoking cessation agent that is targeted towards moderate to heavy smokers (32-34). Therefore, this group of patients provide an ideal study population for evaluating the efficacy and safety of the combination of varenicline and nicotine lozenges for smoking cessation. In addition to this, an inpatient setting allows the trial medications to be commenced and administered under clinical supervision of hospital staff. This would ensure that participants have immediate access to a healthcare professional for medication education or management of an adverse drug event due to any trial medication. This study, therefore, aims to evaluate the effectiveness and safety of the combination of varenicline and NRT lozenges versus varenicline monotherapy in assisting hospitalised smokers in quitting.

Objectives

The primary objective of the study is to compare biochemically-verified continuous abstinence at 6 months in hospitalised smokers treated using varenicline plus NRT lozenges with those treated with varenicline and placebo lozenges.

The secondary objectives of this study are to compare the differences between treatment groups on the following outcomes:

- CO verified continuous abstinence from 2 weeks to 12 months after treatment initiation for participants who self-report abstinence at the 12-month follow-up
- Self-reported 7-day point prevalence abstinence and continuous abstinence measured from 2 weeks to 3, 6 and 12 months after treatment initiation
- CO verified 7-day point prevalence abstinence from 2 weeks to 6 and 12 months after treatment initiation for participants who self-report abstinence at these follow-ups
- Self-reported treatment adherence and adverse events to the study medicines at all follow-ups as well as number of Quitline sessions attended after treatment initiation.

METHODS

Study design

A randomised, placebo-controlled, multi-centre, double blinded study

Setting and Participants

Participants will be recruited from the inpatient wards of five 'smoke-free' public hospitals in Australia. Participants will be screened for eligibility at baseline and written informed consent will be sought. Eligible participants will be randomised to either the intervention or control group and will be followed up for 12 months from treatment initiation.

Inclusion and Exclusion criteria

Patients eligible for the trial are: adults ≥18 years, admitted to participating hospitals with a history of smoking ≥10 cigarettes per day on average in the four weeks prior to their hospital admission, interested in quitting smoking, willing to use pharmacotherapy, available for a 12 months follow-up post-treatment initiation and willing/capable to provide written informed consent.

Patients who do not meet all of the above inclusion criteria, those who have a terminal illness with an anticipated survival of <6 months, those who have an unstable cardiovascular status (recent myocardial infarction or stroke within the past 3 months) or those with a new diagnosis of a major psychiatric illness (e.g. psychosis) within the past 3 months will be excluded from the study. Patients unable to provide informed written consent because of their admitting medical condition or health status at the time of recruitment (e.g. patients in intensive care unit or patients with an acute psychiatric condition) will be excluded from the trial. Patients unable to communicate in English and provide written consent will also be excluded given the potential need to regularly communicate with the investigators during the entire trial period, and the lack of funding for interpreters.

Further exclusion criteria for this study are: women who are pregnant, breastfeeding or planning to become pregnant in the next 6 months and patients who were already using smoking cessation medications or approaches at the time of their hospital admission (i.e. NRT, varenicline, bupropion, clonidine, nortriptyline, or electronic nicotine delivering systems). In addition to this, patients who are currently participating in other smoking cessation programs/studies, those who have completed ≥12 weeks course of varenicline in the 12 months prior to hospitalisation (these patients may have a higher nicotine dependence and may not

respond well to sole varenicline therapy), those who have had intolerable/serious adverse events from the use of varenicline or NRTs in the past, and those who have contraindications for their use (including those using medications known to have major interactions with either varenicline or NRT) will be excluded from the study.

Participant recruitment

Eligible participants will be identified through active screening of hospital records by a trained Research Assistant (RA), a nurse or a pharmacist employed at each site. Ward staff including doctors, nurses, pharmacists and physiotherapists will be informed of the study and asked to refer all patients identified as current smokers to the RA. Flyers containing study information will be displayed in hospital wards to notify inpatients of the study. Flyers will contain the contact information of the RA at the site so that interested patients can discuss the study with them.

Once potential participants are identified, the RA in consultation with the treating medical team will assess each patient's eligibility for the study considering their current health status and any apparent contraindications for the use of varenicline or NRT. Details of this initial medical screening will be recorded by the RA. The RA will then approach eligible patients, describe the project to each potential participant, provide a plain language statement and answer any questions. If the patient is interested in participating, written informed consent will be sought before proceeding with the baseline interview.

Baseline data collection

Each participant will be assigned a study number and baseline data collected. Data gathered during the interview will include information on the participant's smoking habits, previous

attempts at quitting and current willingness/confidence to quit. A detailed medical history (current medical conditions and medications) including the presence of any contraindications or precautions for the use of the study medicines (based on the Product Information Sheets) will be sought. Participants with any exclusion criterion will not be enrolled, and will be referred to Quitline for smoking cessation support. Participants who do not meet any of the exclusion criteria, but who have a specified precaution for the use of the trial medications, will be referred to an in-house clinician for further assessment. The decision on whether to include such participants will be at the discretion of the treating medical team, the RA and the patient based on an evaluation of the potential risks and benefits from participation in the study.

The baseline interview will also involve an assessment of the presence of psychological distress using the Patient Health Questionnaire (PHQ-9). Once baseline data collection is completed, to ensure the safe ongoing delivery of healthcare services to participants, the RA will seek the participants' consent to contact their regular general practitioner (GP) and community pharmacist to inform them of their patient's participation in the study.

Randomisation: allocation concealment and sequence generation

Following the collection of baseline data, participants will be randomised to one of the study arms by a clinical trials pharmacist at each of the five hospitals using a computer-generated randomisation list. Randomisation is stratified by site and random permuted block sizes of two and four will be used. Sealed opaque envelopes will be used for the concealment of treatment allocation. Each site will be provided with 64 envelopes containing group allocation. The clinical trials pharmacist at each site will open the envelopes in a sequential manner when a participant is recruited to identify group allocation. Once a participant's group allocation has been noted along with the study ID, study medicines will be charted on the participant's

medication chart by a clinician involved in the study. The clinical trials pharmacist will then dispense the study medicines as stated in the envelope ([varenicline and NRT lozenges] or [varenicline and placebo lozenges]) and hand these to the RA. The RA will then give the medicines to the participant and provide detailed counselling. Participants will not be told whether they are receiving NRT or placebo lozenges. During hospital stay, the nurse in-charge of the ward will be responsible for daily administration of the medicines to the participant according to standard hospital practice. Participants will be asked to notify a nurse when they wish to have a lozenge (NRT or placebo).

Study arms and medicines

NRT and placebo (mint) lozenges will be repackaged and labelled in sachets containing two 2mg lozenges. For the initial supply, participants will be provided with 12 weeks supply of varenicline and 100 sachets of the NRT/placebo lozenges. The number of lozenges used on average per day will be assessed at the 3-week follow-up. Participants who would like additional supplies of the lozenges can have them delivered to their home by post.

Participants will be advised to commence the trial medication(s) during their hospital stay. The smoke-free policies of Australian hospitals create an environment conducive for abstinence. Therefore, all participants will be asked to reduce their smoking over the first seven days of varenicline treatment and aim to quit completely within two weeks. Patients will be asked to stop smoking in line with the varenicline Product Information Sheet (35). The RA involved in recruitment will provide verbal counselling to the participants on the dosing regimen, common adverse effects of the study medicines, who to contact in the event of an emergency, their contact details and how to obtain renewed supplies of trial medications. Participants will also be given Consumer Medicines Information (CMI) sheets on the study medicines and a lozenge

instruction sheet highlighting key information on the dosing regimen and common adverse effects.

All study medicines (varenicline and the lozenges) will be initially given for a duration of 12 weeks. An additional 12 weeks course of the study medicines (varenicline and the lozenges) will be provided to participants who have ceased smoking during the initial course of treatment and are undergoing concurrent counselling (e.g. Quitline) for smoking cessation. At week 11 of treatment, RAs will contact participants in both treatment arms via telephone. At this time-point, participants who self-report continuous abstinence (i.e. smoking no more than 5 cigarettes between week-2 and week-11 of treatment) will be offered an additional 12 weeks of treatment using the same study medications. Participants will also be asked about their use of the Quitline service since the start of the study. The decision to provide the additional course of treatment will be at the discretion of a clinician at the recruiting site based on the participant's nicotine dependence, adherence to treatment, any adverse effects they may have experienced during the initial course and their severity. Additional supplies of the trial medications will be delivered to the participant's home by post or pick-up will be arranged from the recruiting hospital.

Control arm

Participants randomised to the control group will receive varenicline plus placebo (mint) lozenges. Varenicline will be used at the standard dose as follows: 0.5mg once daily on days 1-3, 0.5mg twice daily on days 4-7 and 1mg twice daily from day 8 onwards for 11 weeks. Participants who continue with an additional 12-week course of varenicline will be advised to continue with the standard maintenance dose of 1mg twice daily for this period as recommended in the Product Information Sheet for Champix (36).

Intervention arm

Participants randomised to the intervention arm will receive varenicline plus NRT lozenges. Varenicline will be used at the standard dose as in the control arm.

NRT/Placebo lozenge dosing schedule (37)

Lozenges will be used by participants only when there is an urge to smoke. Participants will be advised to use a lozenge (2mg) as required when they have an urge to smoke (up to every 1-2 hours initially) and not to use more than 15 lozenges in a day. Participants will also be advised on how to use the lozenges as per the points below:

1. Place one lozenge on the tongue and suck until the taste becomes strong
2. Park the lozenge between the gum and cheek
3. When the taste fades start sucking the lozenge again
4. Repeat this process until the lozenge completely dissolves (it takes about 30 minutes)

Quitline support and text messages

All participants (both intervention and control) will be encouraged to use behavioural support from Quitline as per Quitline standard protocols. However, using Quitline support is not a compulsory requirement for participation in the study.

A Quitline referral form will be completed on behalf of the participant by the RA and sent to Quitline following the baseline interview. Quitline staff will contact the participant in the first instance at a suitable time noted on the referral form. Quitline staff will make a total of four attempts to contact the participant. If a participant is unreachable, Quitline will notify the RA

at the respective site. The RA will follow this up with the participant at the next scheduled follow-up (1 or 3 weeks).

Automated text messages will be sent to all participants by Quitline using their standard procedures i.e. once a week for the first month of treatment, then once every month. Text messages will reinforce the importance of adherence to the study medicines to increase abstinence and also contain emergency contact details for the participants. Participants who do not have a mobile phone will be called (with their permission) on their home phone by the RA instead of sending text messages.

Concomitant treatment

Participants will be able to take any other medicines as required, except for smoking cessation medicines, after discussing with the prescriber of their involvement in the trial. Use of concomitant medicines will be assessed and recorded at each follow-up and verification of any potential interactions with the study medicines will be carried out. The use of other smoking cessation medicines including other forms of NRT (e.g. patches) will be strongly discouraged during the course of the study. If a participant uses other smoking cessation medicines during the study period, an appropriate record of this will be maintained. Data from such participants will still be included in the primary and secondary analyses, however sensitivity analysis will be performed after excluding them from the primary analysis.

Data Collection and follow-up

Baseline data will be collected at the time of recruitment. All participants will be followed up for a period of 12 months after treatment initiation. Five follow-up interviews will be conducted: at weeks one and three of treatment and at three, six and twelve months after the

start of treatment. The first and second follow-ups will be done by the RA and will be conducted face-to-face for participants who are still inpatients, or via telephone for participants who have been discharged. Three-, six- and twelve- month follow-ups will be conducted via telephone by a RA, who is blinded to treatment allocation and who was not involved in participant recruitment. Participants unable to be contacted for follow-ups will be considered as "smokers" according to the Russell Standard (38).

General demographics including age, gender, ethnicity, highest level of education, employment status and possession of any health care card (allowing subsidised health services and medications for the cardholders) will be collected at baseline. Medical and medication history will be obtained from the patients' hospital notes. Smoking-related information such as current smoking status, age at smoking onset, environmental triggers to smoking and previous attempts at smoking cessation will also be gathered. In addition to this, the study will employ the following validated scales:

- ***Heaviness of Smoking Index (HSI):*** the two item scale measures nicotine dependence and considers time to the first cigarette of the day and the number of cigarettes smoked per day (39).
- ***Patient Health Questionnaire (PHQ-9):*** this nine-item scale will be used to measure and monitor symptoms of depression amongst participants. Each item will be scored on a four point scale ranging from 'not at all' to 'nearly every day'(40).
- ***Visual analogue scales*** to assess the participants' level of motivation and confidence to quit smoking: a 10-point numerical scale with one being 'very low' to 10 being 'very high' will be used for participants to self-report their motivation and confidence to quit smoking.

- ***Mood and physical symptoms scale (MPSS):*** This questionnaire assesses the severity of withdrawal symptoms and the strengths and frequencies of patients' urges to smoke. The MPSS involves 5-point ratings of depressed mood, irritability, restlessness, difficulty concentrating and hunger and 6-point ratings of strength of urges to smoke and time spent with urges (41).
- ***Tool for adherence behaviour screening (TABS):*** This is an 8-item tool that assesses both intentional and unintentional non-adherence, participants rate each adherence behaviour statement on a 5-point scale ranging from 'always' to 'never' (42).

Blinding

Three-, six- and twelve- month follow-ups will be conducted by a RA blinded to treatment allocation. Any accidental unblinding will be documented and reported.

Primary endpoints

The primary endpoint is biochemically verified continuous abstinence from 2 weeks to 6 months after treatment initiation. A 2-week period will be allowed on treatment commencement to match the recommended grace period in the varenicline Product Information Sheet (35). Participants who self-report continuous abstinence (i.e. self-report of having smoked no more than five cigarettes, including the use of non-combustible tobacco products and electronic cigarettes) over this period (i.e. weeks 2- 26) will be asked to perform a carbon monoxide (CO) breath test. CO levels will be measured by a trained RA blinded to treatment allocation, using a handheld piCO+ Smokerlyzer (Bedfont Scientific, Maidstone, Kent, UK) during a hospital or home visit. All CO breath testing will be scheduled as soon as is possible (within 1 week) after self-report of abstinence has been recorded. Participants with a CO level <10 ppm will be considered abstinent (18, 43). Sensitivity analysis will be performed using a lower CO cut-off of <5ppm (44).

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Secondary endpoints

The secondary outcomes are:

1) Participant self-reported continuous abstinence from 2 weeks to three, six and twelve months after treatment initiation

2) CO verified continuous abstinence from 2 weeks to 12 months after treatment initiation for participants who self-report abstinence at this follow-up

2) Self-reports of withdrawal symptoms and cravings

3) Self-reports of adherence to varenicline treatment measured using the TABS

4) Self-reports of the number of lozenges consumed per day (NRT or placebo)

5) Change in psychological distress

6) Adverse events experienced from the study medicines

7) Number of Quitline sessions attended/received (self-reported and data transfer from Quitline)

8) Self-reported utilisation of other smoking cessation therapies and alternative products (e.g. electronic cigarettes)

9) Self-reported 7-day point prevalence abstinence (i.e. smoking not even a puff in the past 7 days on the day of follow-up) at 3, 6 and 12 months after treatment initiation

10) CO verified 7-day point prevalence abstinence at 6 and 12 months after treatment initiation for participants who self-report abstinence at these follow-ups

Withdrawal criteria

All participants are strongly encouraged to complete the study, however there may be situations where withdrawal from the study may be appropriate. Participants may withdraw from the study if one or more of the following occur:

- The participant experiences any serious adverse event (SAE) from the use of the study medicines. Prior to treatment discontinuation, input from the treating medical team and Data Safety and Monitoring Board (DSMB) will be sought in establishing the association between treatment exposure and adverse events. The DSMB will review all such cases and make the final judgement on causality.
- If a female participant becomes pregnant during the course of treatment
- If a participant's health status changes significantly and the study medications are no longer in the best interest of the participant
- The lead investigators or health professionals perceive, for any reason, that the study is no longer in the best interest of the participant
- A participant may be withdrawn from the study if he/she wants to do so. Participants are free to withdraw from the study at any time without providing any reason or being disadvantaged.

A participant wishing to withdraw from the study will be asked to complete a 'withdrawal form' for record purposes, but it is not mandatory. Once withdrawn from the study, the participant will not be contacted for further data collection, however the available data will be included in the intention-to-treat analysis. If withdrawal is the result of an adverse drug reaction, the participants will be followed until the adverse reaction resolves or when they return to clinically acceptable medical status.

Sample size

To show an absolute difference of 15% in continuous abstinence rate between study arms (estimate based on continuous abstinence rates in varenicline-NRT trials)(21) at the 5% level of significance with 80% power, we will need 160 subjects per arm. A total of 320 participants will be recruited from the five hospitals, i.e. 64 subjects from each hospital, 32 each in

varenicline monotherapy and varenicline + NRT arms. The primary analysis will be by ITT and participants lost to follow-up will be regarded as smokers (38).

Data analysis

The distribution of data will be assessed and analysed using appropriate statistical tests. Baseline demographic and clinical characteristics will be summarised using counts and proportions, mean and standard deviation or median and interquartile range, according to data type and distribution.

As recommended by the Russell Standard, all randomised patients will be accounted for in the ITT analysis (38). Participants with missing outcomes at follow-up, or whose self-reported abstinence was not biochemically validated will be considered as smokers. Sensitivity analyses using multiple imputation methods will also be carried out. Deceased participants will be excluded from analyses. In a supportive analysis of the primary efficacy endpoint, an analysis will also be conducted on the per protocol set, which excludes patients with any major protocol deviations. Use of NRT after admission to the hospital will be captured and adjusted for in the analysis. Additional unadjusted and adjusted analyses will be performed with analysis by medication status (additional medication given or not given) as a covariate and an interaction of the intervention with this covariate. The statistical analysis plan will be finalised to provide a detailed description of all the analyses prior to locking of the database.

Continuous abstinence at six and twelve months in each treatment arm will be estimated. Differences between arms and the corresponding 95% confidence interval will be determined. Primary analysis will be performed using a cut-off CO of <10ppm and additional sensitivity analysis will be conducted using a lower cut-off of <5ppm (44). Logistic regression models

will be used to examine the efficacy of intervention on the primary outcome, after testing homogeneity between hospitals using a random effects meta-analysis. In the event of heterogeneity, generalised estimating equation models incorporating clustering by hospital will be fitted. The effect of intervention on continuous abstinence at 6 and 12 months will be tested in pre-specified subgroups (per hospital, nicotine dependence, highly motivated versus moderately motivated smokers and men versus women) using models fitted for each subgroup containing main effects for intervention and subgroup and an interaction between them. Statistical significance will be set at a two-sided p value of 0.05.

All randomised participants who take at least one dose of the treatment medications will be included in the safety analysis. A chi-squared test or Fisher's exact test as appropriate will be used to compare the frequency of treatment withdrawal between the intervention and control groups. The number of participants discontinuing treatment prematurely for any reason will be summarised by treatment group and by reasons for discontinuation.

The incidence of all suspected adverse events will be summarised by treatment group under the following categories: type, severity, action taken and outcome. Adverse event reports detailing the relationship of all adverse events that occur in response to the study medication will also be prepared. Severity of adverse events will be reported using the Common Terminology Criteria for Adverse Events (CTCAE) grading scale (v5.0). The causality of the adverse events will be determined using the Naranjo algorithm (45).

Data safety and monitoring board (DSMB)

To ensure the safety of the study participants and protect the scientific integrity of the trial, a three-member independent DSMB together with a study statistician has been established. The

DSMB will periodically review trial safety and outcome data and make recommendations regarding the continuation of the trial based on this information. All serious adverse events (SAEs) will be adjudicated by an end point evaluation committee, which reviews documentation related to the SAE and decides regarding its potential causal relationship with the study drug. Suspected SAEs are also reported as required to the ethics committee of the hospital which enrolled the participant, the human research ethics committee of Monash University, and to the study sponsor. Treatment will be discontinued if there are SAEs or safety concerns relating to the use of the study medicines. Any support necessary to those affected or concerned will be provided independent of the study.

ETHICS AND DISSEMINATION

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2015) and the Australian Code for the Responsible Conduct of Research (2018). Approval has been obtained from the Human Ethics Committees of all the participating hospitals and the University. Written informed consent will be obtained from each participant at the time of recruitment.

Both varenicline and NRT have well established safety and efficacy when used appropriately. However, participant safety may still be a concern, especially in combination. Any potential concerns regarding eligibility will be discussed with the treating medical team. Participants in both arms will be closely monitored for any adverse effects.

All identifiable data will be stored securely, in locked filling cabinets and/or password protected computers at the participating hospital sites or at Monash University. Collected data

will be de-identified, entered into an electronic database and saved on password-protected computers. Participants will receive their CO breath test result immediately after testing. After data analysis, a summary of findings will be sent to participants who requested this information. The research team will submit study findings to peer-reviewed journals. Any protocol changes will be updated on the ANZ Clinical Trials Registry.

PATIENT AND PUBLIC INVOLVEMENT

This research will be done without patient or public involvement. Patients and the public will not be invited to comment on the study design and will not be consulted to develop patient relevant outcomes, interpret the results or contribute to the writing or editing of study documents for readability or accuracy.

DISCUSSION

Abstinence rates are suboptimal despite the wide availability of various smoking cessation therapies (4). A significant number of quit attempts result in failure; despite this no new smoking cessation medication has been approved by the Food and Drugs Administration since varenicline in 2006 (11). Effective combinations of existing smoking cessation therapies are thus needed to further boost abstinence rates.

This is the first multi-centre, placebo-controlled, randomised controlled trial to evaluate the efficacy and safety of a combination of varenicline with acute release forms of NRT. This is also the first pragmatic trial to explore the effectiveness of this combination treatment in achieving long-term abstinence rates among inpatients in Australian hospitals. Varenicline has proven to be one of the most effective smoking cessation therapies, however current literature suggests that it may not completely attenuate nicotine cravings. This effect could be overcome

by the addition of an acute release form of NRT (11, 20). If effective this combination treatment may help to further boost abstinence rates and the results of this trial could help guide future smoking cessation treatments and guidelines. Smoking is banned in the premises of all the participating hospitals. This smoke-free environment will help to promote smoking cessation in both the intervention and the control arms of the study.

Some strengths of the current study include the randomisation of participants to the intervention and control arms reducing selection bias and outcome assessment by staff blinded to treatment allocation. The multi-centre design of the trial will ensure that the study sample is representative of the inpatient smokers who are admitted to Australian public hospitals. It will also enable greater generalisability of the study findings. Furthermore, biochemical verification of abstinence used in this trial will enable us to make accurate inferences regarding the effectiveness of the intervention. According to standard practices, public hospitals in Australia offer NRT to inpatient smokers on admission to help them to abide to the hospital's smoke-free policy. As a result, some participants may already be using NRT (e.g. patch) when they are recruited. This may affect the participant's initial response to the study medication and would be one of the potential limitations of this study. Use of NRT after admission to the hospital will be captured and adjusted for in analysis.

TRIAL STATUS

This trial is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12618001792213). Approval will be sought from the Human Research Ethics Committees of all the participating hospitals and Monash University.

AUTHORS' CONTRIBUTIONS

JG conceived the research idea and developed it with input from other chief investigators, MA, BB, MD, BS, AW and secured research funding. The CIs developed the study in collaboration with GW, SK, OR and AV. RKG is a PhD scholar under the supervision of JG, MA and BB coordinating all the project activities. All the investigators (RKG, MA, BB, GW, MD, BS, AV, AW, SK, DT, AM, RG, EP, JP, DM, LC, ZK, OR, PL, JG) contributed to all phases of the protocol development and finalisation of the manuscript. All authors have reviewed this manuscript and have approved the final protocol.

FUNDING

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COMPETING INTERESTS

Michael Abramson, Billie Bonevski and Johnson George have held investigator-initiated grants from Boehringer Ingelheim (BI) Pty Ltd for an unrelated project. Michael Abramson has also received assistance with conference attendance and conducted an unrelated consultancy for Sanofi. He has also received a speaker's fee from GSK. Johnson George has received honorarium from GSK and Pfizer for consultancy and educational grants for unrelated projects.

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Reporting checklist for protocol of a clinical trial.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4 & 25
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a This is an investigator-initiated trial. The study is supported by a grant awarded by the Global Research Awards for Nicotine dependence 2017.
Roles and	#5d	Composition, roles, and responsibilities of	23

responsibilities: committees		the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	20
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the	16 and 18

		trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a a schematic diagram has not been provided however the process of recruitment, treatment initiation and follow-ups is clearly detailed in the protocol
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21
Recruitment	#15	Strategies for achieving adequate participant	11

		enrolment to reach target sample size	
Methods:			
Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12 & 13
Blinding (masking)	#17a	Who will be blinded after assignment to	18

		interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention	16 & 21

		protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	21

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	23
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility	23

		criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who	20

		suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

The efficacy and safety of varenicline alone versus in combination with nicotine lozenges for smoking cessation among hospitalised smokers (VANISH): study protocol for a randomised, placebo-controlled trial

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Complete List of Authors:	Gobarani, Rukshar; Monash University Faculty of Pharmacy and Pharmaceutical Sciences, Centre for Medicine Use and Safety Abramson, Michael; Monash University School of Public Health and Preventive Medicine Bonevski, Billie; The University of Newcastle, School and Medicine and Public Health Weeks, Gregory; Barwon Health, Pharmacy Department Dooley, Michael; Monash University Faculty of Pharmacy and Pharmaceutical Sciences, Centre for Medicine Use and Safety; Alfred Health, Pharmacy Department Smith, Brian; Bendigo Health - Bendigo Hospital Campus, Department of Clinical Epidemiology and Biostatistics Veale, Antony; The Queen Elizabeth Hospital, Department of Respiratory Medicine Webb, Ashley; Frankston Hospital, Department of Anaesthesia and Pain Management Kirsa, Sue; Monash Health, Pharmacy Thomas, Dennis; The University of Newcastle Hunter Medical Research Institute, Priority Research Centre for Healthy Lungs Miller, Alistair; Royal Melbourne Hospital, Respiratory and Sleep Medicine Gasser, Rudi; Barwon Health, Department of General Medicine Paul, Eldho; Monash University School of Public Health and Preventive Medicine; Alfred Health, Clinical Haematology Department Parkinson, Jacqueline; Monash Health, Pharmacy Department Meanger, Darshana; Frankston Hospital, Pharmacy Department Coward, Lisa; Frankston Hospital, Department of Anaesthesia Kopsaftis, Zoe; The Queen Elizabeth Hospital, Respiratory Medicine and Clinical Practice Unit Rofe, Olivia; Eastern Health Foundation, Pharmacy Department Lee, Paula; Eastern Health Foundation, Pharmacy Department George, Johnson; Monash University Faculty of Pharmacy and Pharmaceutical Sciences, Centre for Medine Use and Safety
Primary Subject Heading:	Smoking and tobacco
Secondary Subject Heading:	Addiction, Public health, Smoking and tobacco

Keywords:	PUBLIC HEALTH, Clinical trials < THERAPEUTICS, PRIMARY CARE

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The efficacy and safety of varenicline alone versus in combination with nicotine lozenges for smoking cessation among hospitalised smokers (VANISH): study protocol for a randomised, placebo-controlled trial

Authors:

Miss Rukshar K. Gobarani, BPharm (Hons), Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; rukshar.gobarani@monash.edu

Prof Michael J. Abramson, PhD, FRACP, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; michael.abramson@monash.edu

Prof Billie Bonevski, PhD, School and Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia; billie.bonevski@newcastle.edu.au

Dr Gregory R. Weeks, PhD, Pharmacy Department, Barwon Health, Geelong, Victoria, Australia; greg@barwonhealth.org.au

Prof Michael J. Dooley, PhD, Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia; Pharmacy Department, The Alfred, Prahran, Victoria, Australia; M.Dooley@alfred.org.au

Prof Brian J. Smith, MBBS, FRACP**,** PhD, Dip Clin Epi and Biostats, Bendigo Hospital, Victoria, Australia; bsmith555@bigpond.com

Dr Antony Veale, MBBS, FRACP, Department of Respiratory Medicine, The Queen Elizabeth Hospital, Adelaide, Australia; antony.veale@sa.gov.au

Dr Ashley Webb, MBBS (Hons)**,** MPH, FANZCA Department of Anaesthesia and Pain Management, Peninsula Health, Frankston, Victoria, Australia; AWebb@phcn.vic.gov.au

A/Prof Sue Kirsa, Grad Dip Hosp Pharm, Pharmacy Department, Monash Health, Clayton, Victoria, Australia; Sue.Kirsa@monash.edu

Dr Dennis Thomas, PhD, Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, University of Newcastle, New South Wales, Australia; dennis.thomas@newcastle.edu.au

Dr Alistair Miller, MBBS, Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Melbourne, Victoria, Australia; alistair.miller3@mh.org.au

Dr Rudi Gasser, MBBS, Department of General Medicine, Barwon Health, Geelong, Victoria, Australia; rudig@barwonhealth.org.au

Dr Eldho Paul, PhD, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; Clinical Haematology Department, The Alfred, Melbourne, Victoria, Australia; eldho.paul@monash.edu

Ms Jacqueline Parkinson, MPharm, Pharmacy Department, Monash Health, Clayton, Victoria, Australia; Jacqueline.Parkinson@monashhealth.org

Miss Darshana Meanger, BPharm, Grad Cert Pharm Prac, Pharmacy Department, Peninsula Health, Frankston, Victoria, Australia; DMeanger@phcn.vic.gov.au

Ms Lisa Coward, EEN, Department of Anaesthesia, Peninsula Health, Frankston, Victoria, Australia; LCoward@phcn.vic.gov.au

Dr Zoe Kopsaftis, PhD, BHSc (Hons), Respiratory Medicine and Clinical Practice Unit, The Queen Elizabeth Hospital, Adelaide, South Australia, Australia; Zoe.Kopsaftis@sa.gov.au

Ms Olivia Rofe, BPharm, MPharm (Clin), Prof Cert Health Syst Management, Pharmacy Department, Eastern Health, Melbourne, Victoria, Australia; Olivia.Rofe@easternhealth.org.au

Ms Paula Lee, BPharm, Grad Dip Clin Res, Pharmacy Department, Eastern Health, Box Hill, Victoria, Australia; Paula.Lee@easternhealth.org.au

Dr Johnson George ***(corresponding author)***, PhD, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; johnson.george@monash.edu

ABSTRACT

Introduction: Smoking is a leading cause of premature deaths globally. The health benefits of smoking cessation are many. However, majority of quit attempts are unsuccessful. One way to potentially improve success rates is to evaluate new combinations of existing smoking cessation therapies that may work synergistically to decrease the intensity of withdrawal symptoms and cravings.

Aims: To evaluate the feasibility, efficacy and safety of the combination of varenicline and nicotine replacement therapy (NRT) lozenges versus varenicline alone in assisting hospitalised smokers to quit.

Methods and analysis: This is a multi-centre, randomised, placebo-controlled trial. Adults with a history of smoking ≥10 cigarettes per day on average in the four weeks prior to their hospitalisation will be recruited. Participants will be randomly assigned to either the intervention group and will receive varenicline and NRT lozenges, or the control group and will receive varenicline and placebo lozenges. All participants will be actively referred to behavioural support from telephone Quitline. Participants are followed up at 1 and 3 weeks and 3, 6 and 12 months from the start of treatment. The primary outcome is carbon monoxide (CO) validated prolonged abstinence from 2 weeks to 6 months after treatment initiation. Secondary outcomes include self-reported and biochemically validated prolonged and point prevalence abstinence at 3, 6 and 12 months, self-reported adverse events, withdrawal symptoms and cravings, adherence to treatment, Quitline sessions attended etc. According to

the Russell standard, all randomised participants will be accounted for in the primary intention-to-treat analysis.

Ethics and dissemination: The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice, the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2015) and the Australian Code for the Responsible Conduct of Research (2018). Approval will be sought from the Human Ethics Committees of all the participating hospitals and the University. Written informed consent will be obtained from each participant at the time of recruitment.

Trial registration: Australia New Zealand Clinical Trials Registry: ACTRN12618001792213

Strengths and limitations of this study:

- This is the first multi-centre, randomised, placebo-controlled trial to evaluate the efficacy and safety of a combination of varenicline and an immediate-release form of NRT.
- This is also the first pragmatic trial exploring the effectiveness of this combination treatment in achieving long-term abstinence rates among inpatients in Australian hospitals.
- The multi-centre pragmatic design of the trial will ensure that the study sample is representative of the inpatient smokers who are admitted to Australian public hospitals allowing greater generalizability of study findings
- Biochemical verification of abstinence used in this trial will enable us to make accurate inferences regarding the effectiveness of the intervention.

BACKGROUND

Tobacco smoking is one of the leading causes of preventable morbidity and mortality around the world. Representing a key risk factor for deaths due to ischaemic heart disease, stroke and cancer, tobacco smoking kills approximately six million people globally each year.(1) Holding the potential to damage nearly every organ system in the human body, tobacco smoking accounts for 7.8% of the total burden of disease in Australia.(1, 2) Despite this, 14% of adults aged 18 years and over smoked daily in 2017-2018.(2)

Various therapeutic agents are currently available to assist in quitting smoking. A substantial body of research has demonstrated the effectiveness of such therapies in increasing abstinence rates.(3) Of these, varenicline is the most effective single agent for abstinence outcomes. Available as a prescription only medicine in Australia, varenicline at the standard dose more than doubles the chances of quitting compared with placebo (pooled RR for continuous or sustained abstinence at six months or longer 2.24; 95% CI 2.06 to 2.43).(4) It has a dual mechanism of action and exerts its effects by acting as a partial agonist at the α4β2 nicotinic receptors in the brain.(5) This reduces the drop in the mesolimbic dopaminergic levels that occurs during smoking cessation, relieving withdrawal symptoms.(5) Varenicline also antagonises the activity of nicotine on its receptors which prevents the release of neurotransmitters such as dopamine and in doing so reduces feelings of pleasure experienced from a smoking relapse.(5)

Nicotine replacement therapy (NRT) is another first line treatment for those seeking pharmacological help to quitting smoking.(3) NRT replaces some of the nicotine in the blood that was previously derived from cigarettes, without the presence of the thousands of other chemicals that are also produced during tobacco combustion which are largely responsible for

causing tobacco-related illnesses.(6, 7) In this manner, NRT decreases the intensity of withdrawal symptoms and cigarette cravings.(6, 7)

In many countries, NRT is available over-the-counter in acute release formulations such as gums, lozenges, inhalers, mouth sprays and sublingual tablets and in slow release forms such as transdermal patches. Transdermal patches release nicotine slowly over a prolonged period of time (24 or 16 hour patches available) whereas, acute release forms of NRT provide a faster release of nicotine in the blood.(6) Acute-dosing products allow the user to titrate both the amount and timing of their doses.(6) Therefore, these forms of NRT can be used as "rescue-medication" by smokers to alleviate cigarette cravings.(6)

NRTs are more effective than placebo in achieving long-term smoking abstinence (RR of abstinence for any form of NRT relative to control 1.55; 95% CI 1.49 to 1.61).(8) Various forms of NRT perform similarly against each other [pooled RRs of 1.64 for nicotine patch (95% CI 1.53 to 1.75); 1.49 for nicotine gum (95% CI 1.40 to 1.60) and 1.52 for oral tablets/lozenges (95% CI 1.32 to 1.74) relative to control], and evidence suggests that the use of two forms of NRT; a slow release formulation with an acute release formulation (i.e. combination NRT) is more effective than using a single form of NRT.(3)

Research to date suggests that varenicline (as monotherapy) and combination NRT are the most effective smoking cessation therapies that are currently available to assist in achieving abstinence.(3) Even these, however, result in only modest increases in abstinence rates of approximately 30-40% at 6 months compared with placebo.(4, 9-11) A substantial amount of research is thus focused on evaluating new treatment options and approaches for smoking cessation to further increase abstinence rates.(12)

In attempts to improve smoking cessation rates, new combinations of existing smoking cessation therapies have been evaluated.(13-15) Current research suggests that varenicline may not fully saturate the nicotinic acetylcholine receptors in the brain.(13) This in turn leads to only a partial attenuation of nicotine cravings.(16) It has been postulated that adding NRT to varenicline treatment may therefore increase receptor saturation, which in turn may decrease cigarette cravings more completely.(13, 16)

In response to this, studies have evaluated the effectiveness of the combination of varenicline and NRT patches versus varenicline monotherapy on smoking cessation rates, although findings have been equivocal.(16, 17) A systematic review and meta-analysis of three randomised controlled trials demonstrated that the combination of varenicline and NRT patches was associated with significantly higher rates of abstinence versus varenicline alone at the end of treatment i.e. at 12 weeks (OR 1.50; 95% CI 1.14 to 1.97) and at 6 months (OR 1.62; 95% CI 1.18 to 2.23).(18) This association, however, did not exist when the largest of the three trials, which also used a pre-quit nicotine patch, was excluded from the analysis.(18)

No studies to date have evaluated the effectiveness of the combination of varenicline and acute release forms of NRT which have proven to be just as effective as NRT patches in assisting smokers to quit.(8) Secondly, steady-state plasma varenicline concentrations are achieved after approximately four days of continued treatment.(13) During this time, patients may experience significant discomfort from withdrawal symptoms and often continue to smoke for several weeks after initiating varenicline therapy.(13) Furthermore, a study reported that while varenicline reduces both tonic and cue-induced cigarette cravings, it does not attenuate cue-induced cravings after stress induction compared to placebo.(19) In such situations, the use of an *ad lib* NRT product in combination with varenicline would thus enable patients to better

manage their withdrawal symptoms and cravings particularly to prevent stress and cue-related reinstatement of smoking.(13, 19)

Smoking inside public hospitals and within 4 meters of the entrances to all public hospitals is prohibited in Australia.(20) This restriction provides a window of opportunity for the implementation of smoking cessation interventions as inpatient smokers are placed away from their usual environmental triggers of smoking. During this time of increased vulnerability regarding their health, patients may be more motivated to quit and may also be more receptive to smoking cessation interventions and a change in behaviour particularly if they are presenting with conditions that may be caused or exacerbated by smoking.(21-25)

Furthermore, hospitalised inpatients generally smoke a greater number of cigarettes per day than the general population and have a higher level of nicotine dependence.(1, 26) Varenicline is a smoking cessation agent that is targeted towards moderate to heavy smokers.(27-29) Therefore, this group of patients provide an ideal study population for evaluating the efficacy and safety of the combination of varenicline and nicotine lozenges for smoking cessation. In addition to this, an inpatient setting allows the trial medications to be commenced and administered under clinical supervision of hospital staff. This would ensure that participants have immediate access to a healthcare professional for medication education or management of an adverse drug event due to any trial medication. This study, therefore, aims to evaluate the effectiveness and safety of the combination of varenicline and NRT lozenges versus varenicline monotherapy in assisting hospitalised smokers in quitting.

Objectives

The primary objective of the study is to compare biochemically-verified prolonged abstinence at 6 months in hospitalised smokers treated using varenicline plus NRT lozenges with those treated with varenicline and placebo lozenges.

The secondary objectives of this study are to compare the differences between treatment groups on the following outcomes:

- CO verified prolonged abstinence from 2 weeks to 12 months after treatment initiation for participants who self-report abstinence at the 12-month follow-up
- Self-reported 7-day point prevalence abstinence (smoking not even a puff in the past 7 days on the day of follow-up) at 3, 6 and 12 months after treatment initiation
- Self-reported prolonged abstinence measured from 2 weeks to 3, 6 and 12 months after treatment initiation
- CO verified 7-day point prevalence abstinence at 6 and 12 months after treatment initiation for participants who self-report abstinence at these follow-ups
- Self-reported treatment adherence and adverse events to the study medicines at all follow-ups as well as number of Quitline sessions attended after treatment initiation.

METHODS

Study design

A randomised, placebo-controlled, multi-centre, double blinded study

Setting and Participants

Participants will be recruited from the inpatient wards of five ‘smoke-free’ public hospitals in Australia. Participants will be screened for eligibility at baseline and written informed consent

will be sought. Eligible participants will be randomised to either the intervention or control group and will be followed up for 12 months from treatment initiation.

Inclusion and Exclusion criteria

Patients eligible for the trial are: adults ≥18 years, admitted to participating hospitals with a history of smoking ≥10 cigarettes per day on average in the four weeks prior to their hospital admission, interested in quitting smoking, willing to use pharmacotherapy, available for a 12 months follow-up post-treatment initiation and willing/capable to provide written informed consent.

Patients who do not meet all of the above inclusion criteria, those who have a terminal illness with an anticipated survival of <6 months, those who have an unstable cardiovascular status (recent myocardial infarction or stroke within the past 3 months) or those with a new diagnosis of a major psychiatric illness (e.g. psychosis) within the past 3 months will be excluded from the study. Patients unable to provide informed written consent because of their admitting medical condition or health status at the time of recruitment (e.g. patients in intensive care unit or patients with an acute psychiatric condition) will be excluded from the trial. Patients unable to communicate in English and provide written consent will also be excluded given the potential need to regularly communicate with the investigators during the entire trial period, and the lack of funding for interpreters.

Further exclusion criteria for this study are: women who are pregnant, breastfeeding or planning to become pregnant in the next 6 months and patients who were already using smoking cessation medications or approaches at the time of their hospital admission (i.e. NRT, varenicline, bupropion, clonidine, nortriptyline, or electronic nicotine delivering systems). In

addition to this, patients who are currently participating in other smoking cessation programs/studies, those who have completed ≥12 weeks course of varenicline in the 12 months prior to hospitalisation (these patients may have a higher nicotine dependence and may not respond well to sole varenicline therapy), those who have had intolerable/serious adverse events from the use of varenicline or NRTs in the past, and those who have contraindications for their use (including those using medications known to have major interactions with either varenicline or NRT) will be excluded from the study.

Participant recruitment

Eligible participants will be identified through active screening of hospital records by a trained Research Assistant (RA), a nurse or a pharmacist employed at each site. Ward staff including doctors, nurses, pharmacists and physiotherapists will be informed of the study and asked to refer all patients identified as current smokers to the RA. Flyers containing study information will be displayed in hospital wards to notify inpatients of the study. Flyers will contain the contact information of the RA at the site so that interested patients can discuss the study with them.

Once potential participants are identified, the RA in consultation with the treating medical team will assess each patient's eligibility for the study considering their current health status and any apparent contraindications for the use of varenicline or NRT. Details of this initial medical screening will be recorded by the RA. The RA will then approach eligible patients, describe the project to each potential participant, provide a plain language statement and answer any questions. If the patient is interested in participating, written informed consent will be sought before proceeding with the baseline interview.

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Baseline data collection

Each participant will be assigned a study number and baseline data collected. Data gathered during the interview will include information on the participant's smoking habits, previous attempts at quitting and current willingness/confidence to quit. A detailed medical history (current medical conditions and medications) including the presence of any contraindications or precautions for the use of the study medicines (based on the Product Information Sheets) will be sought. Participants with any exclusion criterion will not be enrolled, and will be referred to Quitline for smoking cessation support. Participants who do not meet any of the exclusion criteria, but who have a specified precaution for the use of the trial medications, will be referred to an in-house clinician for further assessment. The decision on whether to include such participants will be at the discretion of the treating medical team, the RA and the patient based on an evaluation of the potential risks and benefits from participation in the study.

The baseline interview will also involve an assessment of the presence of psychological distress using the Patient Health Questionnaire (PHQ-9). Once baseline data collection is completed, to ensure the safe ongoing delivery of healthcare services to participants, the RA will seek the participants' consent to contact their regular general practitioner (GP) and community pharmacist to inform them of their patient's participation in the study.

Randomisation: allocation concealment and sequence generation

Following the collection of baseline data, participants will be randomised to one of the study arms by a clinical trials pharmacist at each of the five hospitals using a computer-generated randomisation list. Randomisation is stratified by site and random permuted block sizes of two and four will be used. Sealed opaque envelopes will be used for the concealment of treatment allocation. Each site will be provided with 64 envelopes containing group allocation. The

clinical trials pharmacist at each site will open the envelopes in a sequential manner when a participant is recruited to identify group allocation. Once a participant's group allocation has been noted along with the study ID, study medicines will be charted on the participant's medication chart by a clinician involved in the study. The clinical trials pharmacist will then dispense the study medicines as stated in the envelope ([varenicline and NRT lozenges] or [varenicline and placebo lozenges]) and hand these to the RA. The RA will then give the medicines to the participant and provide detailed counselling. Participants will not be told whether they are receiving NRT or placebo lozenges. During hospital stay, the nurse in-charge of the ward will be responsible for daily administration of the medicines to the participant according to standard hospital practice. Participants will be asked to notify a nurse when they wish to have a lozenge (NRT or placebo).

Study arms and medicines

Participants randomised to the control group will receive varenicline plus placebo (mint) lozenges while participants randomised to the intervention arm will receive varenicline plus NRT lozenges.

Varenicline in both treatment arms will be used at the standard dose as follows: 0.5mg once daily on days 1-3, 0.5mg twice daily on days 4-7 and 1mg twice daily from day 8 onwards for 11 weeks.(30) Participants who continue with an additional 12-week course of varenicline will be advised to continue with the standard maintenance dose of 1mg twice daily for this period as recommended in the Product Information Sheet for Champix.(30)

NRT/Placebo lozenge dosing schedule

Lozenges will be used by participants only when there is an urge to smoke.(31) Participants will be advised to use a lozenge (2mg) as required when they have an urge to smoke (up to every 1-2 hours initially) and not to use more than 15 lozenges in a day.(31) Participants will also be advised on how to use the lozenges as per the points below:

1. Place one lozenge on the tongue and suck until the taste becomes strong
2. Park the lozenge between the gum and cheek
3. When the taste fades start sucking the lozenge again
4. Repeat this process until the lozenge completely dissolves (it takes about 30 minutes)

NRT and placebo (mint) lozenges will be repackaged and labelled in sachets containing two 2mg lozenges. For the initial supply, participants will be provided with 12 weeks supply of varenicline and 100 sachets of the NRT/placebo lozenges. The number of lozenges used on average per day will be assessed at the 3-week follow-up. Participants who would like additional supplies of the lozenges can have them delivered to their home by post.

Participants will be advised to commence the trial medication(s) during their hospital stay. The smoke-free policies of Australian hospitals create an environment conducive for abstinence. However, this does not prevent inpatient smokers from going outside hospital premises for a smoke. Therefore, all participants will be asked to reduce their smoking over the first seven days of varenicline treatment and aim to quit completely within two weeks. Patients will be asked to stop smoking in line with the varenicline Product Information Sheet.(30) The RA involved in recruitment will provide verbal counselling to the participants on the dosing regimen, common adverse effects of the study medicines, who to contact in the event of an emergency, their contact details and how to obtain renewed supplies of trial medications. Participants will also be given Consumer Medicines Information (CMI) sheets on the study

medicines and a lozenge instruction sheet highlighting key information on the dosing regimen and common adverse effects.

All study medicines (varenicline and the lozenges) will be initially given for a duration of 12 weeks. An additional 12 weeks course of the study medicines (varenicline and the lozenges) will be provided to participants who have ceased smoking during the initial course of treatment and are undergoing concurrent counselling (e.g. Quitline) for smoking cessation. At week 11 of treatment, RAs will contact participants in both treatment arms via telephone. At this time-point, participants who self-report prolonged abstinence (i.e. smoking no more than 5 cigarettes between week-2 and week-11 of treatment) will be offered an additional 12 weeks of treatment using the same study medications. Participants will also be asked about their use of the Quitline service since the start of the study. The decision to provide the additional course of treatment will be at the discretion of a clinician at the recruiting site based on the participant's nicotine dependence, adherence to treatment, any adverse effects they may have experienced during the initial course and their severity. Additional supplies of the trial medications will be delivered to the participant's home by post or pick-up will be arranged from the recruiting hospital.

Quitline support and text messages

All participants (both intervention and control) will be encouraged to use behavioural support from Quitline as per Quitline standard protocols. However, using Quitline support is not a compulsory requirement for participation in the study.

A Quitline referral form will be completed on behalf of the participant by the RA and sent to Quitline following the baseline interview. Quitline staff will contact the participant in the first instance at a suitable time noted on the referral form. Quitline staff will make a total of four

attempts to contact the participant. If a participant is unreachable, Quitline will notify the RA at the respective site. The RA will follow this up with the participant at the next scheduled follow-up (1 or 3 weeks).

Automated text messages will be sent to all participants by Quitline using their standard procedures i.e. once a week for the first month of treatment, then once every month. Text messages will reinforce the importance of adherence to the study medicines to increase abstinence and also contain emergency contact details for the participants. Participants who do not have a mobile phone will be called (with their permission) on their home phone by the RA instead of sending text messages.

Concomitant treatment

Participants will be able to take any other medicines as required, except for smoking cessation medicines, after discussing with the prescriber of their involvement in the trial. Use of concomitant medicines will be assessed and recorded at each follow-up and verification of any potential interactions with the study medicines will be carried out. The use of other smoking cessation medicines including other forms of NRT (e.g. patches) will be strongly discouraged during the course of the study. If a participant uses other smoking cessation medicines during the study period, an appropriate record of this will be maintained. Data from such participants will still be included in the primary and secondary analyses, however sensitivity analysis will be performed after excluding them from the primary analysis.

Data Collection and follow-up

Baseline data will be collected at the time of recruitment. All participants will be followed up for a period of 12 months after treatment initiation. Five follow-up interviews will be

conducted: at weeks one and three of treatment and at three, six and twelve months after the start of treatment. The first and second follow-ups will be done by the RA and will be conducted face-to-face for participants who are still inpatients, or via telephone for participants who have been discharged. Three-, six- and twelve- month follow-ups will be conducted via telephone by a RA, who is blinded to treatment allocation and who was not involved in participant recruitment. Participants unable to be contacted for follow-ups will be considered as "smokers" according to the Russell Standard.(32)

General demographics including age, gender, ethnicity, highest level of education, employment status and possession of any health care card (allowing subsidised health services and medications for the cardholders) will be collected at baseline. Medical and medication history will be obtained from the patients' hospital notes. Smoking-related information such as current smoking status, age at smoking onset, environmental triggers to smoking and previous attempts at smoking cessation will also be gathered. In addition to this, the study will employ the following validated scales:

- ***Heaviness of Smoking Index (HSI):*** the two item scale measures nicotine dependence and considers time to the first cigarette of the day and the number of cigarettes smoked per day.(33)
- ***Patient Health Questionnaire (PHQ-9):*** this nine-item scale will be used to measure and monitor symptoms of depression amongst participants. Each item will be scored on a four point scale ranging from 'not at all' to 'nearly every day.'(34)
- ***Visual analogue scales*** to assess the participants' level of motivation and confidence to quit smoking: a 10-point numerical scale with one being 'very low' to 10 being 'very high' will be used for participants to self-report their motivation and confidence to quit smoking.

- ***Mood and physical symptoms scale (MPSS):*** This questionnaire assesses the severity of withdrawal symptoms and the strengths and frequencies of patients' urges to smoke. The MPSS involves 5-point ratings of depressed mood, irritability, restlessness, difficulty concentrating and hunger and 6-point ratings of strength of urges to smoke and time spent with urges.(35)
- ***Tool for adherence behaviour screening (TABS):*** This is an 8-item tool that assesses both intentional and unintentional non-adherence, participants rate each adherence behaviour statement on a 5-point scale ranging from 'always' to 'never.'(36)

Blinding

Three-, six- and twelve- month follow-ups will be conducted by a RA blinded to treatment allocation. Any accidental unblinding will be documented and reported.

Primary endpoints

The primary endpoint is biochemically verified prolonged abstinence from 2 weeks to 6 months after treatment initiation. A 2-week period will be allowed on treatment commencement to match the recommended grace period in the varenicline Product Information Sheet.(30) Participants who self-report prolonged abstinence (i.e. self-report of having smoked no more than five cigarettes, including the use of non-combustible tobacco products and electronic cigarettes) over this period (i.e. weeks 2- 26) will be asked to perform a carbon monoxide (CO) breath test. CO levels will be measured by a trained RA blinded to treatment allocation, using a handheld piCO+ Smokerlyzer (Bedfont Scientific, Maidstone, Kent, UK) during a hospital or home visit. All CO breath testing will be scheduled as soon as is possible (within 1 week) after self-report of abstinence has been recorded. Participants with a CO level <6 ppm will be

considered abstinent.(15, 37) Sensitivity analysis will be performed using a higher CO cut-off of <10ppm.(38)

Secondary endpoints

The secondary outcomes are:

1) Participant self-reported prolonged abstinence from 2 weeks to three, six and twelve months after treatment initiation

2) CO verified prolonged abstinence from 2 weeks to 12 months after treatment initiation for participants who self-report abstinence at this follow-up

2) Self-reports of withdrawal symptoms and cravings

3) Self-reports of adherence to varenicline treatment measured using the TABS

4) Self-reports of the average number of lozenges consumed per day (NRT or placebo) at 3-weeks from treatment initiation

5) Change in psychological distress measured using the PHQ-9 scale

6) Adverse events experienced from the study medicines

7) Number of Quitline sessions attended/received (self-reported and data transfer from Quitline)

8) Self-reported utilisation of other smoking cessation therapies and alternative products (e.g. electronic cigarettes)

9) Self-reported 7-day point prevalence abstinence (i.e. smoking not even a puff in the past 7 days on the day of follow-up) at 3, 6 and 12 months after treatment initiation

10) CO verified 7-day point prevalence abstinence at 6 and 12 months after treatment initiation for participants who self-report abstinence at these follow-ups

Withdrawal criteria

All participants are strongly encouraged to complete the study, however there may be situations where withdrawal from the study may be appropriate. Participants may withdraw from the study if one or more of the following occur:

- The participant experiences any serious adverse event (SAE) from the use of the study medicines. Prior to treatment discontinuation, input from the treating medical team and Data Safety and Monitoring Board (DSMB) will be sought in establishing the association between treatment exposure and adverse events. The DSMB will review all such cases and make the final judgement on causality.
- If a female participant becomes pregnant during the course of treatment
- If a participant's health status changes significantly and the study medications are no longer in the best interest of the participant
- The lead investigators or health professionals perceive, for any reason, that the study is no longer in the best interest of the participant
- A participant may be withdrawn from the study if he/she wants to do so. Participants are free to withdraw from the study at any time without providing any reason or being disadvantaged.

A participant wishing to withdraw from the study will be asked to complete a 'withdrawal form' for record purposes, but it is not mandatory. Once withdrawn from the study, the participant will not be contacted for further data collection, however the available data will be included in the intention-to-treat analysis. If withdrawal is the result of an adverse drug reaction, the participants will be followed until the adverse reaction resolves or when they return to clinically acceptable medical status.

Sample size

In a previous trial of hospitalised smokers with high nicotine dependence, the long-term abstinence rate in the usual care and intervention groups were 8.5 – 10%, respectively.(39) Modelling continuous abstinence rates over time from clinical trials of varenicline found that, at 52 weeks, abstinence rates were 22.5% for varenicline and 8.3% for placebo.(40) To show an absolute difference of 15% in prolonged abstinence rate between study arms (estimate based on abstinence rates in varenicline-NRT trials),(17) at the 5% level of significance with 80% power, we will need 160 subjects per arm. A total of 320 participants will be recruited from the five hospitals, i.e. 64 subjects from each hospital, 32 each in varenicline monotherapy and varenicline + NRT arms. The primary analysis will be by ITT and participants lost to follow-up will be regarded as smokers.(32)

Data analysis

The distribution of data will be assessed and analysed using appropriate statistical tests. Baseline demographic and clinical characteristics will be summarised using counts and proportions, mean and standard deviation or median and interquartile range, according to data type and distribution.

As recommended by the Russell Standard, all randomised patients will be accounted for in the ITT analysis.(32) Participants with missing outcomes at follow-up, or whose self-reported abstinence was not biochemically validated will be considered as smokers. Sensitivity analyses using multiple imputation methods will also be carried out. Deceased participants will be excluded from analyses. In a supportive analysis of the primary efficacy endpoint, an analysis will also be conducted on the per protocol set, which excludes patients with any major protocol deviations. Use of NRT after admission to the hospital will be captured and adjusted for in the analysis. Additional unadjusted and adjusted analyses will be performed with analysis by

medication status (additional medication given or not given) as a covariate and an interaction of the intervention with this covariate. The statistical analysis plan will be finalised to provide a detailed description of all the analyses prior to locking of the database.

Prolonged abstinence at six and twelve months in each treatment arm will be estimated. Differences between arms and the corresponding 95% confidence interval will be determined. Primary analysis will be performed using a cut-off CO of <6ppm and additional sensitivity analysis will be conducted using a higher cut-off of <10ppm.(38) Logistic regression models will be used to examine the efficacy of intervention on the primary outcome, after testing homogeneity between hospitals using a random effects meta-analysis. In the event of heterogeneity, generalised estimating equation models incorporating clustering by hospital will be fitted. The effect of intervention on prolonged abstinence at 6 and 12 months will be tested in pre-specified subgroups (per hospital, nicotine dependence, highly motivated versus moderately motivated smokers and men versus women) using models fitted for each subgroup containing main effects for intervention and subgroup and an interaction between them. Statistical significance will be set at a two-sided p value of 0.05.

All randomised participants who take at least one dose of the treatment medications will be included in the safety analysis. A chi-squared test or Fisher's exact test as appropriate will be used to compare the frequency of treatment withdrawal between the intervention and control groups. The number of participants discontinuing treatment prematurely for any reason will be summarised by treatment group and by reasons for discontinuation.

The incidence of all suspected adverse events will be summarised by treatment group under the following categories: type, severity, action taken and outcome. Adverse event reports

detailing the relationship of all adverse events that occur in response to the study medication will also be prepared. Severity of adverse events will be reported using the Common Terminology Criteria for Adverse Events (CTCAE) grading scale (v5.0). The causality of the adverse events will be determined using the Naranjo algorithm.(41)

Data safety and monitoring board (DSMB)

To ensure the safety of the study participants and protect the scientific integrity of the trial, a three-member independent DSMB together with a study statistician has been established. The DSMB will periodically review trial safety and outcome data and make recommendations regarding the continuation of the trial based on this information. All serious adverse events (SAEs) will be adjudicated by an end point evaluation committee, which reviews documentation related to the SAE and decides regarding its potential causal relationship with the study drug. Suspected SAEs are also reported as required to the ethics committee of the hospital which enrolled the participant, the human research ethics committee of Monash University, and to the study sponsor. Treatment will be discontinued if there are SAEs or safety concerns relating to the use of the study medicines. Any support necessary to those affected or concerned will be provided independent of the study.

ETHICS AND DISSEMINATION

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (updated 2015) and the Australian Code for the Responsible Conduct of Research (2018). Approval has been obtained from the Human Ethics Committees of all the participating hospitals and the University. Written informed consent will be obtained from each participant at the time of recruitment.

Both varenicline and NRT have well established safety and efficacy when used appropriately. However, participant safety may still be a concern, especially in combination. Any potential concerns regarding eligibility will be discussed with the treating medical team. Participants in both arms will be closely monitored for any adverse effects.

All identifiable data will be stored securely, in locked filling cabinets and/or password protected computers at the participating hospital sites or at Monash University. Collected data will be de-identified, entered into an electronic database and saved on password-protected computers. Participants will receive their CO breath test result immediately after testing. After data analysis, a summary of findings will be sent to participants who requested this information. The research team will submit study findings to peer-reviewed journals. Any protocol changes will be updated on the ANZ Clinical Trials Registry.

PATIENT AND PUBLIC INVOLVEMENT

This research will be done without patient or public involvement. Patients and the public will not be invited to comment on the study design and will not be consulted to develop patient relevant outcomes, interpret the results or contribute to the writing or editing of study documents for readability or accuracy.

DISCUSSION

Abstinence rates are suboptimal despite the wide availability of various smoking cessation therapies. A significant number of quit attempts result in failure; despite this no new smoking cessation medication has been approved by the Food and Drugs Administration since

varenicline in 2006. Effective combinations of existing smoking cessation therapies are thus needed to further boost abstinence rates.

This is the first multi-centre, placebo-controlled, randomised controlled trial to evaluate the efficacy and safety of a combination of varenicline with acute release forms of NRT. This is also the first pragmatic trial to explore the effectiveness of this combination treatment in achieving long-term abstinence rates among inpatients in Australian hospitals. Varenicline has proven to be one of the most effective smoking cessation therapies, however current literature suggests that it may not completely attenuate nicotine cravings.(12) This effect could be overcome by the addition of an acute release form of NRT.(12, 16) If effective this combination treatment may help to further boost abstinence rates and the results of this trial could help guide future smoking cessation treatments and guidelines. Smoking is banned in the premises of all the participating hospitals. This smoke-free environment will help to promote smoking cessation in both the intervention and the control arms of the study.

Some strengths of the current study include the randomisation of participants to the intervention and control arms reducing selection bias and outcome assessment by staff blinded to treatment allocation. The multi-centre design of the trial will ensure that the study sample is representative of the inpatient smokers who are admitted to Australian public hospitals. It will also enable greater generalisability of the study findings. Furthermore, biochemical verification of abstinence used in this trial will enable us to make accurate inferences regarding the effectiveness of the intervention. According to standard practices, public hospitals in Australia offer NRT to inpatient smokers on admission to help them to abide to the hospital's smoke-free policy.(42) As a result, some participants may already be using NRT (e.g. patch) when they are recruited. This may affect the participant's initial response to the study medication and

would be one of the potential limitations of this study. Use of NRT after admission to the hospital will be captured and adjusted for in analysis.

TRIAL STATUS

This trial is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12618001792213). Approval will be sought from the Human Research Ethics Committees of all the participating hospitals and Monash University.

AUTHORS' CONTRIBUTIONS

JG conceived the research idea and developed it with input from other chief investigators, MA, BB, MD, BS, AW and secured research funding. The CIs developed the study in collaboration with GW, SK, OR and AV. RKG is a PhD scholar under the supervision of JG, MA and BB coordinating all the project activities. All the investigators (RKG, MA, BB, GW, MD, BS, AV, AW, SK, DT, AM, RG, EP, JP, DM, LC, ZK, OR, PL, JG) contributed to all phases of the protocol development and finalisation of the manuscript. All authors have reviewed this manuscript and have approved the final protocol.

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COMPETING INTERESTS

Michael Abramson, Billie Bonevski and Johnson George have held investigator-initiated grants from Boehringer Ingelheim (BI) Pty Ltd for an unrelated project. Michael Abramson

has also received assistance with conference attendance and conducted an unrelated consultancy for Sanofi. He has also received a speaker's fee from GSK. Johnson George has received honorarium from GSK and Pfizer for consultancy and educational grants for unrelated projects.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4 & 25
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a This is an investigator-initiated trial. The study is supported by a grant awarded by the Global Research Awards for Nicotine dependence 2017.
Roles and	#5d	Composition, roles, and responsibilities of	23

responsibilities: committees		the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	20
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the	16 and 18

		trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a a schematic diagram has not been provided however the process of recruitment, treatment initiation and follow-ups is clearly detailed in the protocol
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21
Recruitment	#15	Strategies for achieving adequate participant	11

		enrolment to reach target sample size	
Methods: **Assignment of interventions (for controlled trials)**			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12 & 13
Blinding (masking)	#17a	Who will be blinded after assignment to	18

		interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention	16 & 21

		protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	21

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	23
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility	23

		criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who	20

		suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a