A randomised controlled trial evaluating the effectiveness and tolerability of step-up and step-down varenicline therapy for smoking cessation: Study protocol

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ABSTRACT

Background: Varenicline remains the most effective medication for smoking cessation, however discontinuation as a result of adverse events negatively impacts medication adherence, and the likelihood of a quit attempt being successful. Post treatment cravings and withdrawal symptoms may also occur, increasing the likelihood of treatment failure, due to lapse and relapse after achieving initial abstinence. This protocol details a trial investigating changes in the effectiveness and tolerability of varenicline, when an extended step-up and step-down regimen are used.

Methods: A phase 4, randomised, double-blinded, placebo-controlled single-centre study with a treatment period of 16 weeks, and follow-up period of 12 weeks will be conducted. Up to 201 participants will be enrolled and allocated in a 1:1:1 ratio to a placebo-matching control group, step-up, or step-down intervention group, all receiving behavioural counselling and quitting advice. Participants will be contacted weekly during treatment and fortnightly during follow-up. Eligible participants are smokers over 18 years old, willing to quit smoking, are able to attend clinic visits, and have no uncontrolled or serious medical issues. Primary outcome measures are comparisons of biochemically confirmed continuous abstinence rates, 7-day point prevalence abstinence rates and the frequency, severity and duration of adverse events, cravings and withdrawal symptoms. Secondary outcome measures are participant adherence to the study medication throughout treatment, and comparisons of changes in smoking satisfaction and reward. Effects of each regimen on smoking cessation will be assessed by logistic regression, with survival analyses used for a more precise estimate of when cessation occurs. Primary endpoints will then be compared using a general linear model. Australian New Zealand Clinical Trials Registry: ACTRN12616000802404p

INTRODUCTION

Tobacco use continues to be a major contributor to preventable morbidity and mortality, being strongly linked to a growing list of health conditions, including several forms of cancer, and cardiovascular and respiratory diseases (Fiore *et al*., 2008). Unfortunately, successful smoking cessation continues to be challenging, despite the availability of smoking cessation medications and behavioural counselling techniques (Cahill *et al*., 2013). Medications such as varenicline (Champix® / Chantix®), the most effective agent available for smoking cessation (Cahill *et al*., 2016), have several clinical issues impacting on their effectiveness such as causing intolerable adverse effects leading to premature therapy discontinuation, poor adherence, and a resurgence of cravings and withdrawal symptoms after therapy has been completed (Drovandi *et al*., 2016; Balmford *et* al., 2011; Catz *et al*., 2011; Liberman *et al*., 2013; Rigotti *et al*., 2010).

Modifications to the varenicline regimen through changes in daily dosing may address these problems as suggested by a recent systematic review (Drovandi *et al*., 2017). Modifications trialled and warranting further study include the use of an extended duration of pre-quit varenicline therapy (Hajek *et al*., 2011; Hawk *et al*., 2012), and an extended duration of varenicline therapy (Tonstad *et al*., 2006; Williams *et al*., 2007). These modifications were theorised to reduce the frequency and severity of adverse events at the beginning of therapy and the long-term risk of relapse at the end of treatment. A modification yet to be tested is a step-down period at the end of varenicline therapy, potentially reducing the short-term risk of relapse at the end of treatment, which has been encountered in some clinical trials (Tonstad *et al*., 2006; Rigotti *et al*., 2010).

This protocol was developed to evaluate changes in the effectiveness and tolerability of varenicline, when it is introduced more slowly over a period of 4 weeks and ceased over a period of 2 weeks. It is proposed that the use of extended 'step-up' therapy will reduce the frequency and severity of adverse effects, which are usually more prominent at the beginning of therapy (Tonstad *et al.,* 2016; Williams *et al*., 2007), and the use of 'step-down' therapy will reduce the likelihood of recurring

cravings and withdrawal symptoms due to a sudden drop in dopamine levels from the removal of varenicline (Coe *et al.,* 2005).

METHODS

This protocol has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616000802404p), and was developed to comply with the Helsinki Declaration of 1975 (revised in 2008) and Australian Guidelines on the development of ethical research. Ethical approval was given by the James Cook University's Human Research Ethics Committee (approval number H6748). This article for the study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Chan *et al*., 2013).

Study Design

A randomised, double-blinded, placebo-controlled trial will consist of three treatment groups with different dosing schedules: two intervention groups (step-up and step-down varenicline therapies) and a placebo-matched control group. This community-based single-site trial will require participants to adhere to a treatment duration of 16-weeks and a follow-up duration of 12-weeks, and attend scheduled clinic visits at James Cook University's Health Clinic in Townsville, Australia.

Participant Eligibility and Recruitment

Eligible participants are required to be at least 18 years old and motivated to quit smoking, have a Fagerström Test for Nicotine Dependence (FTND) score of at least 5.0, indicate their intention to comply with scheduled clinic visits, have no history of major or uncontrolled depressive or other psychiatric disorders, and use appropriate hormonal contraception if a woman of childbearing age. Participants are ineligible if they have a history of a suicide attempt or any suicidal behaviours in the previous 2 years, have a severe or uncontrolled major depressive, psychiatric, or cardiovascular disorder, have a current psychosis, have concomitant substance abuse disorders, have used varenicline within the previous 6 months, or do not agree to abstain from non-cigarette tobacco products during the intervention and follow-up periods.

Participants will be recruited from pharmacies, general practitioner clinics and newspaper advertisements in Townsville, Australia. Potential participants may view, self-assess and complete an expression of interest flyer at these locations, which include preliminary eligibility questions, and the contact details of the principal investigator to facilitate a baseline visit with the potential participant. Final eligibility and further information and consent documents will be provided during the baseline visit to ensure the eligibility and safety of participants.

Treatment Groups and Interventions

The dose regimens for all the treatment groups are detailed in **Table** 1. Intervention group 1 (step-up) will be assigned to take 0.5mg once daily for 7 days, 0.5mg twice daily for 7 days, 0.5mg once daily plus 1.0mg once daily for 7 days, 1.0mg twice daily for 11 weeks, then 2 weeks of placebo tablets matched to the step-down intervention group. Intervention group 2 (step-down) will be assigned to take 2 weeks of placebo tablets matched to the step-up intervention group, followed by 0.5mg once daily for 3 days, 0.5mg twice daily for 4 days, 1.0mg twice daily for 11 weeks, then 0.5mg twice daily for 7 days, then 0.5mg once daily for 7 days. The control group will be assigned to take 2 weeks of placebo tablets matched to the step-up intervention group, followed by 0.5mg once daily for 3 days, 0.5mg twice daily for 4 days, 1.0mg twice daily for 11 weeks, then 2 weeks of placebo tablets matched to the step-down intervention group. The medication provided will be supplied in a dose administration aid (DAA) to avoid dosing confusion, maintain treatment blinding, and to serve as a mechanism for monitoring participant adherence (Haywood and Glass, 2016).

Eligible participants will be randomly assigned a participant identifier number (PIN), each of which is linked through a computer-generated randomisation sequence to a treatment group. Treatment allocations will be sealed in individual envelopes, and a research associate who is not involved in the study will be responsible for affixing PINs to each DAA to ensure continued double-blinding. However, a participant's allocated treatment can be revealed prior to completion of the study, if the participant experiences a life-threatening or other severe event.

Interventions for eligible participants for the duration of the trial, including data collection tools are detailed in **Tables 2** and **3** for the treatment and follow-up periods respectively. Participants will be contacted weekly during the treatment phase, and fortnightly during the follow-up phase through a combination of telephone calls and face to face clinic visits. These scheduled interactions will gather data on participant health indicators (both physical and mental), concomitant medication load, adverse events, cravings and withdrawal symptoms experienced, and recent smoking habits. Participants will receive a booklet on smoking cessation during the baseline visit, and up to 10 minutes of individualised counselling on techniques for smoking cessation during each intervention, and be recommended to set a quit date between weeks 4 and 6 of treatment.

Study Outcomes

Primary outcomes to be assessed during this trial are comparisons of biochemically confirmed continuous abstinence rates, 7-day point prevalence abstinence rates and the frequency, severity, and duration of adverse effects, cravings, and withdrawal symptoms. These primary outcomes will determine if step-up or step-down varenicline dosing has positive effects as measured by improved smoking cessation rates and reduced adverse events, cravings, or withdrawal symptoms during cessation attempts. Secondary outcome measures include adherence to the study medication throughout treatment and changes in smoking satisfaction and reward.

Data Collection and Management

During the interventional and follow-up periods, as detailed in **Table 2** and **Table 3** respectively**,** data for the primary and secondary outcomes will be initially collected from participants on a weekly basis, with monthly face to face clinic visits being interspersed by telephone calls. Adverse events. Continuous and 7-day point prevalence abstinence rates will be assessed by multiple methods, including the Nicotine Use Inventory (NUI), a personal smoking log, and biochemically confirmed using a Micro+ Smokerlyzer device. The NUI will be administered during scheduled telephone and clinic visits by the principal investigator, querying the participants' use of cigarettes or any other nicotine-containing products. The smoking log will be used daily by participants to track their exposure to nicotine throughout the treatment and follow-up periods, and reported

abstinence to be confirmed during clinic visits using a Micro+ Smokerlyzer device, with a cut-off reading of <10ppm considered as being abstinent. All adverse events, including serious and non-serious, will be recorded on case report forms on a per-participant basis, to be reported to the principal investigator, and causality determined during the scheduled telephone and face to face clinic visits. Participants will be encouraged to log adverse events daily as they occur, ensuring to note changes in severity or apparent cause if they persist over several days, will be coded using MedDRA, and followed-up until cessation of the event. Concerning or unusual adverse events will be reported immediately to the principal investigator, with events considered to be serious or unexpected to also be reported to Pfizer Inc., the approving ethics committee, and the Adverse Drug Reaction unit of the Therapeutic Goods Administration. Physical health will be assessed at the commencement and cessation of treatment, and at the completion of the follow-up period, and include recording of participant height, weight, and vital signs (blood pressure, respiratory rate, and heart rate). Mental health will be assessed initially using the Suicide Behaviours Questionnaire Revised (SBQ-R) (Osman et al., 2001), and monitored fortnightly using the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). The 9-item version of the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1986) will be used to assess weekly changes in cravings and withdrawal symptoms, using a 5-point Likert scale ranging from 0 (not at all) to 5 (extreme). The MNWS will be self-administered by participants on a daily basis, and reported to the principal investigator during phone calls and clinic visits.

Medication adherence checks will be done by the principal investigator during the treatment period clinic visits, by counting remaining tablets in returned DAAs. Changes in smoking satisfaction and reward will be assessed by the principal investigator using the Modified Cigarette Evaluation Questionnaire (mCEQ) (Cappelleri et al., 2007), a 12-item questionnaire rating on a 7-point scale from 1 (Not at all) to 7 (Extremely) the common experiences normally received by smoking. All data collection will be performed by the principal investigator only, who will personally enter all data into a master excel spreadsheet, which will be stored on a passwordprotected computer in the office of the principal investigator. PINs will be used in this spreadsheet to ensure confidentiality.

Sample Size and Statistical Analyses

Using GPOWER v3.1, it was determined that to detect a moderate effect size with 80% power, a total of 119 completers are required for statistical power for the primary endpoints of the study, being the biochemically confirmed continuous abstinence rate for participants in each treatment group. To ensure statistical power is achieved, up to 201 participants will be enrolled to accommodate up to 40% participant withdrawal from treatment and loss to follow-up as demonstrated by similarly designed smoking cessation trials (Hajek *et al*., 2011; Rigotti *et al*., 2010; Hawk *et al*., 2012). Intention to treat analysis will include univariate and multivariate analysis of the factors associated with abstinence post-quit date. Analysis will occur after the final participant has completed their end-of-study clinic visit.

Data analysis will include assessing biochemically confirmed continuous abstinence rates and the presence of, and numerical scale of severity of adverse events, cravings and withdrawal symptoms, for smokers or non-smokers. Quantitative data will be subjected to multivariate analysis in SPSS (v23) to establish relationship between categorical and continuous variables. Logistic regression will be used to assess the effect of the treatment regimens on smoking cessation. Odds ratio (OR) will be used to compare the relative odds of occurrence of smoking cessation, between the active and control groups. The 95% confidence intervals (CI) will be used to estimate the precision of the OR. Survival analysis (via cox regression) will be used to measure more precise and absolute estimates of when smoking cessation occurs. A survival probability estimate will also be calculated using the Kaplan-Meier method. Survival curves and a non-parametric statistical log rank test will be used to determine significant differences between the groups. The severity of adverse events, cravings and withdrawal symptoms will be compared between the three groups, using a General Linear Model (GLM) in SPSS (v23). Significance levels were set at 0.05 and a medium effect size as reported by Cohen (1988) will be calculated to determine the magnitude of statistically significant relationships. No interim analyses are planned for this study.

Study Monitoring

Adverse event-recording documents will be provided both electronically and as hard-copies during clinic visits, and when additionally requested. Participants who experience intolerable adverse events or worsening of concomitant medical conditions may have their dose temporarily reduced or withdrawn, with recommencing of the standard dose at the discretion of the participant, principal investigator, and medical advisor. Participants may also have treatment permanently withdrawn if their participation places them at an excessive risk of harm (including changes in behaviour or mood), or demonstrate an inability to comply with the study protocol. Participants will be encouraged to log adverse events daily, which will be regularly monitored by the principal investigator, to track event progression and ensure the resolution of events.

ETHICS AND DISSEMINATION

This research has been approved by the James Cook University Human Research Ethics Committee (approval number H6748), with amendments to the protocol submitted to the committee and to Pfizer Inc. as they occur. The principal investigator will be responsible for gaining informed consent from participants and will maintain patient confidentiality during clinic visits and phone calls. Advisors to the principal investigator will only have access to de-identified data from participants. Results for this research will largely be disseminated through publication in peer-reviewed journals. The approving ethics committee, Pfizer Inc., and the supplier of the dose administration aids (Webstercare) will be provided with detailed reports on the outcomes of the research, and participants will be offered a report of the research if desired.

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Table 1. Varenicline dosing schedules for the three treatment regimens.

Treatment Group	Week 1	Week 2	Week 3	Weeks 4-14	Week 15	Week 16	Weeks 17-28
Intervention Group 1	0.5mg once daily (morning)	0.5mg twice daily	1.0mg morning, 0.5mg night	1.0mg twice daily	Placebo twice daily	Placebo once daily (morning)	Follow-up phase
Intervention Group 2	Placebo* once daily (morning)	Placebo twice daily	0.5mg morning for 3 days, 0.5mg twice daily for 4 days	1.0mg twice daily	0.5mg twice daily	0.5mg once daily (morning)	Follow-up phase
Control Group	Placebo once daily (morning)	Placebo twice daily	0.5mg morning for 3 days, 0.5mg twice daily for 4 days	1.0mg twice daily	Placebo twice daily	Placebo once daily (morning)	Follow-up phase

* Only 0.5mg-tablet matching placebos will used during the study

Table 2. Schedule of procedures between the principal investigator and study participants during the treatment period.

Participant Activity	Screening	BL	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16
Window	2 weeks	-	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days
Interaction Type	-	CV	TC	TC	TC	CV	TC	TC	TC	CV	TC	TC	TC	CV	TC	TC	TC	CV
EOI Flyer	X																	
Participant Information	X	X																
Risks and Benefits	X	X																
Informed Consent	X	X																
Medical History		X																
FTND		X																
SBQ-R		X																
Baseline Details Demographics		X																
Smoking history		X																
Carbon Monoxide Test		X				X				X				X				X
Height/weight		X																X
Vitals		X																X
Randomisation		X																
PIN assigned		X																
PHQ-9		X		X		X		X		X		X		X		X		X
NUI			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Provided		X				X				X				X				
mCEQ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MNWS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Counselling (<10 minutes)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
'Quit Because You Can' Booklet		X																
Adherence Recording						X				X				X				X
Smoking Log		X	X	X	X	X	X	X										

BL: Baseline CV: Clinic Visit TC: Telephone Call EOI: Expression of Interest FTND: Fagerström Test for Nicotine Dependence SBQ-R: Suicide Behaviours Questionnaire Revised PIN: Participant Identifier Number
PHQ-9: Patient Health Questionnaire-9 NUI: Nicotine Use Inventory mCEQ: Modified cigarette evaluation questionnaire MNWS: Minnesota Nicotine Withdrawal Scale

Table 3. Schedule of procedures between the principal investigator and participants during the follow-up period

Participant Activity	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26	Week 27	Week 28
Window	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days
Interaction Type	N/A	TC	N/A	TC	N/A	CV	N/A	TC	N/A	TC	N/A	CV
Carbon Monoxide Test						X						X
Height/weight												X
Vitals												X
PHQ-9		X		X		X		X		X		X
NUI		X		X		X		X		X		X
Concomitant Medications		X		X		X		X		X		X
mCEQ		X		X		X		X		X		X
Adverse Events		X		X								
MNWS		X		X		X		X		X		X
Counselling (<10 minutes)		X		X		X		X		X		X

CV: Clinic Visit TC: Telephone Call PHQ-9: Patient Health Questionnaire-9 NUI: Nicotine Use Inventory
mCEQ: Modified cigarette evaluation questionnaire MNWS: Minnesota Nicotine Withdrawal Scale