



# Efficacy of smoking cessation with varenicline plus counselling for e-cigarettes users (VAREVAPE): A protocol for a randomized controlled trial

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## ABSTRACT

Tobacco smoking is a global pandemic that poses substantial health burdens and costs. With nearly six million deaths annually, smoking is the single most important cause of avoidable premature mortality in the world, mainly from lung cancer, coronary heart disease, chronic obstructive pulmonary disease and stroke. Smoking is a very difficult addiction to break, even for those with a strong desire to quit. Electronic cigarettes are an attractive long-term alternative source of nicotine to conventional cigarettes because of their many similarities with smoking. Electronic cigarette users report buying them to reduce cigarette consumption, to relieve tobacco withdrawal symptoms, to quit, and to continue having a 'smoking' experience, but with reduced health risks. Actually, there aren't antismoking treatments for people who smoke only electronic cigarette (single users) or electronic cigarette and classic cigarette (dual users). There isn't any specific information on the efficacy and safety of new pharmacological support for electronic cigarette users. We propose that smoking cessation with varenicline plus counselling delivered to electronic cigarette users could be associated with similar smoking abstinence rates compared to the results obtained in the general population. Herein, we describe the methodology of a double-blind, placebo-controlled, randomized clinical trial, of 24 weeks duration, that examines the efficacy of varenicline (1 mg BID - for 12 weeks) plus counselling compared to matched placebo (1 mg BID - for 12 weeks) plus counselling.

## 1. Introduction

Tobacco smoking is a global pandemic, affecting an estimated 1.2 billion people, that poses substantial health burdens and costs [1]. With nearly six million deaths annually, smoking is the single most important cause of avoidable premature mortality in the world, mainly from lung cancer, coronary heart disease, chronic obstructive pulmonary disease and stroke [1]. As also underscored by the World Health Organization Framework Convention on Tobacco Control, the key to reducing the health burden of tobacco in the medium term is to encourage cessation among smokers [2]. Unfortunately, smoking is a very difficult addiction to break, even for those with a strong desire to quit. It has been shown that approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence, and only about 5% achieve long term abstinence [3]. Electronic cigarettes are an attractive long-

term alternative source of nicotine to conventional cigarettes because of their many similarities with smoking. E-cigarettes users report buying them to reduce cigarette consumption, to relieve tobacco withdrawal symptoms, to quit, and to continue having a 'smoking' experience, but with reduced health risks [4]. There aren't antismoking treatments for people who smoke only electronic cigarette (single users) or electronic cigarette and classic cigarette (dual users). Surprisingly, there aren't data available in the literature on smoking cessation intervention for this specific disease group and also, no specific information on the efficacy and safety of new pharmacological support for electronic cigarettes users.

Varenicline is a partial agonist of the  $\alpha 4 \beta 2$  nicotinic acetylcholine receptor that causes partial stimulation while it competitively inhibits nicotine binding. Recently, randomized, controlled clinical trials have shown that varenicline at a dose of 1 mg twice a day is superior to

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placebo for smoking cessation [5,6]. Varenicline appears to be also more effective than sustained-release bupropion [7]. Data from these trials indicate that the most common adverse event attributed to varenicline at a dose of 1 mg twice daily is nausea [5–7]. However, the efficacy and safety of varenicline has never been tested in electronic cigarette users interested in stopping e-cigarettes and only a recent study investigated if ‘dual users’ who smoke and use e-cigarettes are interested in stopping smoking by using varenicline [8]. However, question arises whether people who smoke only electronic cigarette (single users) or electronic cigarette and classic cigarette (dual users) could benefit from using an integrated smoking cessation programme that combine varenicline plus smoking cessation counselling. Dual use is an emerging phenomenon and while there is no consensus on its definition, in most evidence-based literature it is commonly referred to as those who use both e-cigarettes and classic cigarettes whereas those who smoke only e-cigarettes are referred to as single [9]. While traditional cigarette combustion generates toxic substances correlated with cancers, respiratory and cardiovascular disorders, long term e-cigarettes usage could determine adverse events such as mouth and throat irritation and or a psychological need in the vaper to no longer use the e-cigarette to be free from any form of possible nicotinic addiction.

Therefore, we designed a randomized controlled study to test the effectiveness of a smoking cessation programme with varenicline in electronic cigarette users. We hypothesized that smoking cessation with varenicline could be associated with similar smoking abstinence rates compared to the results obtained in the general population. Given that a better understanding of predictors of smoking cessation can be useful in identifying potential quitters and likely relapsers [10] and that little is known about these predictors in e-cigarettes users, the role of different predictors of abstinence at the end of the study will also be examined.

## 2. Design and methods

### 2.1. Overview and design

The study is a double-blind, placebo-controlled, randomized clinical trial. It will be designed as a parallel two-group RCT of 24 weeks duration with participants being randomized to either counselling + varenicline (1 mg BID) for 12 weeks or to counselling + matched placebo. The duration of active treatment will be 12 weeks.

A final visit is scheduled for week 24; abstinence from smoking and vaping will be recorded and evaluated objectively by the levels of saliva cotinine. Vital signs and weight will be measured. This final visit will be conducted by a researcher who is not aware of the group allocation of the study participants.

### 2.2. Outcome measures

The primary outcome for the study is a comparison of varenicline to placebo for the Continuous Abstinence Rate (CQR) for Weeks 9 through 24. This measure will be obtained through reports of cigarette, e-cigarette and other nicotine use since the last study visit confirmed by a measurement of an end-expiratory exhaled carbon monoxide concentration that is  $\leq 10$  ppm and by saliva cotinine levels. Cotinine saliva levels will be measured to further objectively verify smoking status. A cut off of  $< 7$  ng/ml of cotinine will distinguish smokers from nonsmokers.

Additional study outcomes measures of interest will be: 1. Safety end-points for varenicline; 2. Predictors of abstinence (e.g. gender, age at smoking initiation, previous quit attempts, FTCD, motivation, depression, anxiety, social/familial environment, etc.) at the end of the study; 3. Percentage of participants' retention in the study.

Safety end-points: 1. Adverse events: Adverse events (AEs) observed or reported will be recorded on the case report form. Assessments as to seriousness, severity, and the relationship to treatment and other causes

will be made. Serious adverse events (SAEs) will also be captured in the centralized database. AEs and SAEs will be reported to the appropriate regulatory agency(ies); 2. Physical Examination: Physical examination will be performed at the screening visit and at Week 12; 3. Blood pressure, pulse rate, and temperature: Blood pressure and pulse rate will be measured at all clinic visits. Temperature will be measured at the baseline visit; 4. Electrocardiogram: An electrocardiogram will be obtained at screening; 5. Body weight: Body weight will be measured at all visits. It will be measured in indoor clothing without shoes.

### 2.3. Overview of intervention

Before the baseline visit, a face to face screening (V0) for pre-eligibility checks will be conducted.

At screening visit, participants will be seen in a screening visit, during which informed consent will be obtained prior to any study procedures. Physical examination, blood pressure, pulse rate cardiologic visit and electrocardiogram will be done. A serum pregnancy test will be completed for all females at the screening.

At baseline visit a standardized questionnaire will be used to collect relevant information on: 1) sociodemographic factors: age, sex, level of education, and marital status; 2) history of tobacco use: number of daily smoked cigarettes, years of smoking, pack/years, smoking status of other members of the household, previous quit attempts; 3) motivation score by visual analogic score, nicotine dependence by FTCD and e-cigarettes dependence by Penn State Electronic Cigarette Dependence Index; 4) depression and anxiety will be assessed by Beck Depression Inventory (BDI) and by Beck Anxiety Inventory (BAI) respectively. BMI (obtained from the patients' clinical diary) will also be recorded. Concentration of monoxide carbon will be also measured.

Participants will be then instructed on how to prepare to stop smoking and to set a quit date. A serum pregnancy test will be completed for all females.

Each participant will be randomly assigned to either varenicline 1 mg BID + counselling or matched placebo + counselling using a form of adaptive randomization designed to minimize imbalances in the distribution of prognostic factors (gender, depression, motivation, previous quit attempts, and level of nicotine dependence) between study groups. The randomized assignment will be blinded.

All participants will be offered smoking cessation counselling over several brief (10–20 min) office appointments.

Visits from week 1 to week 12. The first follow up appointment will be timed within 48 h from the set quit date. On each occasion, self-reported smoking status will be checked and verified by saliva cotinine, occurrence of tobacco withdrawal symptoms (such as anxiety, restlessness, poor concentration, irritability, insomnia, depression, craving, stypsis and increased appetite) evaluated, adherence to medication reviewed, and any difficulty related to their smoking cessation efforts discussed in detail. The Week 1 visit must be scheduled to occur 8 days after the baseline visit, so that subjects have a full 7 days of treatment prior to the TQD (target quit date). Subjects will return for visits to the clinic after the baseline visit over the following 12 weeks at Weeks 1, 2, 3, 4, 8 and 12. Subsequent to Week 1, visits will occur within 3 days of each scheduled visit date. The subjects will attempt to quit on the target quit date at the Week 1 visit (8 days after the baseline visit). All concomitant medications and any adverse events will be recorded. Vital signs and weight will be measured. Exclusively at week 12 a serum pregnancy test will be completed for all females.

Varenicline should be discontinued immediately if patients show agitation, depressed mood, or changes in behaviour that create concerns in the doctor, the patient, family or those who take care of the patient, or if the patient develops suicidal ideation or suicidal behaviour.

Non-treatment Follow-up (Weeks 13 through 24). Participants will attend a final visit (week 24); abstinence from smoking and vaping will be recorded and objectively assessed by saliva cotinine levels. Vital

signs and weight will be measured. This final visit will be conducted by a physician who is unaware of the group allocation of the study participants.

## 2.4. Study schedule

Screening visit (V1): Screening visit for eligibility criteria. Will be delivered informed consent will be obtained prior to any study procedures. Physical examination, blood pressure, pulse rate cardiological visit and electrocardiogram will be done. A serum pregnancy test will be completed for all females at the screening (Table 1).

Baseline (Visit 2): a standardized questionnaire will be used to collect relevant information on: 1) sociodemographic factors: age, sex, level of education, and marital status; 2) history of tobacco use: number of daily smoked cigarettes, years of smoking, pack/years, smoking status of other members of the household, previous quit attempts; 3) motivation score by visual analog score, nicotine dependence by FTND and e-cigarette dependence by Penn State Electronic Cigarette Dependence Index; 4) depression and anxiety assessed by Beck Depression Inventory (BDI) and by Beck Anxiety Inventory (BAI) respectively. BMI (obtained from the patients' clinical diary) will also be recorded. Concentration of monoxide carbon will be also measured. Participants will be then instructed on how to prepare to stop smoking and to set a quit date. A serum pregnancy test will be completed for all females.

Each participant will be randomly assigned to either varenicline 1 mg BID + counselling or matched placebo + counselling using a form of adaptive randomization designed to minimize imbalances in the distribution of prognostic factors (gender, depression, motivation, previous quit attempts, and level of nicotine dependence) between study groups. The randomized assignment will be blinded.

All participants will be offered smoking cessation counselling over several brief (10–20 min) office appointments (Table 1).

Visit 3: self-reported smoking status will be checked and verified by

saliva cotinine, occurrence of tobacco withdrawal symptoms (such as anxiety, restlessness, poor concentration, irritability, insomnia, depression, craving, stypsis and increased appetite) evaluated, adherence to medication reviewed, and any difficulty related to their smoking cessation efforts discussed in detail (Table 1).

Visit 4: during this visit these parameters will be evaluated: ECO (exhaled Carbon Monoxide), Counselling, Dispense study drug, Smoking status, Saliva cotinine (in case of self-declaration of quitting), Minnesota Nicotine Withdrawal Scale, Adherence to medication, Adverse events, Concomitant medication, Vital signs (temperature only BL), and Weight (Table 1).

Visit 5: during this visit these parameters will be evaluated: ECO (exhaled Carbon Monoxide), Counseling, Dispense study drug, Smoking status, Saliva cotinine (in case of self-declaration of quitting), Minnesota Nicotine Withdrawal Scale, Adherence to medication, Adverse events, Concomitant medication, Vital signs (temperature only BL), and Weight (Table 1).

Visit 6: during this visit these parameters will be evaluated: ECO (Exhaled Carbon Monoxide), Counseling, Dispense study drug, Smoking status, Saliva cotinine (in case of self-declaration of quitting), Minnesota Nicotine Withdrawal Scale, Adherence to medication, Adverse events, Concomitant medication, Vital signs (temperature only BL), and Weight (Table 1).

TC 1: it consists of a telephone contact in which the participant will be asked to report his smoking status and offered counselling.

Visit 7: during this visit these parameters will be evaluated: ECO (exhaled Carbon Monoxide), Counseling, Dispense study drug, Smoking status, Saliva cotinine (in case of self-declaration of quitting), Minnesota Nicotine Withdrawal Scale, Adherence to medication, Adverse events, Concomitant medication, Vital signs (temperature only BL), and Weight (Table 1).

TC 2: it consists of a telephone contact in which the participant will be asked to report his smoking status and offered counselling.

Visit 8: at week 12 a serum pregnancy test will be completed for all

**Table 1**  
Study schedule/flowchart.

Procedure	Screen	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 12
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	TC	VISIT 5	TC	VISIT 6	TC	VISIT 7	VISIT 8
Physical examination and cardiological visit (ECG).	X										
Informed consent											
Medical history		X									
Smoking history		X									
Vital signs (HR, BP, WEIGHT)	X	X	X	X	X	X		X		X	X
Sociodemographic factors		X									
Adverse events		X	X	X	X	X	X	X	X	X	X
Antidiabetic drug use		X	X	X	X	X	X	X	X	X	X
FTND		X									
Motivation by VAS		X									
BDI & BAI		X									
GN-SBQ		X									
Nicotine Use Inventory		X	X	X	X	X	X	X	X	X	X
Blood chemistry, CBC		X		X							X
Urinalysis		X		X							X
DM lab tests		X									
Pregnancy test	X										
eCO		X	X	X	X	X		X		X	X
Counseling		X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X		X		X	
Dosing record			X	X	X	X		X		X	X

BL = baseline; TC = telephone contact; HR = heart rate; BP = blood pressure.

FTND = Fagerstrom Test for Nicotine Dependence; VAS = visual analog score.

BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory.

eCO = exhaled carbon monoxide.

Wk1 must be scheduled 8 days after the baseline visit.

Dispense study drug – a week supply of drug/placebo is dispensed at each visit with the exception of Wk 4, Wk 6, Wk 8 and Wk 10 when a whole 2 weeks supply is given.

**Table 2**  
Non-treatment follow-up Schedule.

Procedure	Wk24 Clinic Visit
	VISIT 9
Nicotine Use	X
Inventory	
Vital signs (HR, BP, WEIGHT)	X
eCO	X
Antidiabetic drug use	X
Counseling	X
Saliva tests	X

females. Moreover, the parameters of ECO (exhaled Carbon Monoxide), Counseling, Smoking status, Saliva cotinine (in case of self-declaration of quitting), Minnesota Nicotine Withdrawal Scale, Adherence to medication, Adverse events, Concomitant medication, Vital signs (temperature only BL), and Weight (Table 1).

TC 3: it consists of a telephone contact in which the participant will be asked to report his/her smoking status and offered counselling.

Visit 9: Participants will attend a final visit 9 (week 24); abstinence from smoking and vaping will be recorded and objectively assessed by saliva cotinine levels. Vital signs and weight will be measured. This final visit will be conducted by a physician who is unaware of the group allocation of the study participants (Table 2).

## 2.5. Active intervention

Varenicline was discovered through the synthesis of a series of compounds inspired by the natural product, cytisine, which was previously known to have partial agonist activity at the  $\alpha 4\beta 2$  nAChR [5]. Varenicline was found to be a selective partial agonist at the  $\alpha 4\beta 2$  nAChR, displaying ~30–60% of the in vivo efficacy of nicotine, and it also effectively blocked the in vivo response to nicotine [5]. Varenicline has been available as a pharmacotherapy for smoking cessation since 2006. Smoking cessation by the help of varenicline is accepted as a reliable monotherapy to provide high smoking abstinence rates [6]. Varenicline is selective partial agonist of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor [7]. Among patients not able to quit smoking, use of varenicline for 24 weeks significantly increased smoking cessation [8].

Administration: Treatment will begin on the day after the baseline visit. The subjects will take a total of one 0.5 mg tablets per day for the first 3 days of the dosing period. In the morning, the first blinded varenicline tablet on the dosing cards will be taken. The dosing will then increase for the next 4 days to two tablets per day, 1 in the morning and 1 in the evening. The dosing will then increase to four tablets per day, 2 in the morning and 2 in the evening for the remainder of the study.

## 2.6. Participants

140 Caucasian e-cigarettes users, vaping nicotine-containing liquids daily for > 3 months (single users); and 140 Caucasian ecigs users, vaping nicotine-containing liquids daily for > 3 months; who also smoke at least one conventional cig/day (i.e. dual users) and willing to quit, will be invited to participate in the study.

Inclusion Criteria: Male or female ages of 18 and 75 years, inclusive, who are motivated to stop smoking. Females of nonchildbearing potential (surgically sterilized or at least 2 years postmenopausal) who are not nursing may be included. Females of childbearing potential may be included provided that they are not pregnant, not nursing, and are practicing effective contraception and meet all of the following criteria:

1. Are instructed and agree to avoid pregnancy through 30 days after the last dose of study medication,

2.7. Have a negative serum pregnancy test ( $\beta$ -hCG) at screening and baseline, and

3. Agree to use one of the birth control methods listed below:

- an oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive, or an injectable contraceptive for at least one month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication,
- a barrier method of contraception, e.g., condom and/or diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication.

Exclusion Criteria: Patients with a history of alcoholism; History of epilepsy; Comorbid psychiatric disorders (Schizophrenia, Major Depression, Bipolar Disorder); History of psychiatric disorders; History of suicide attempts within the past three months and/or current suicidal ideation/plan and subjects at risk for the development of depressive symptom; Pregnant and breastfeeding women will be excluded: Patients with severe renal impairment and symptomatic vascular disease (including a history of ischaemic heart disease, stroke) will be also excluded from the study.

## 2.8. Statistical methods

Though inferences will be model based, sample sizes are approximated based on the comparison of varenicline 1 mg BID vs placebo, using a two-group continuity-corrected Chi-Squared test with a 0.050 two-sided significance level. The sample size calculation for this RCT, based on the expected cessation rates from our previous smoking cessation study, indicates that a totally of 138 subjects will be required to have 80% power with two-sided 0.05 significance level test to detect a difference of at least 20% quit rate between treatment groups [11]. Allowing for a conservative attrition rate of 50%, the target number of participants will be increased to a total of 276.

Baseline and demographic data will be listed for all treatment groups. Summary statistics will be provided for each treatment group.

Safety data will be subjected to clinical review and summarized by frequencies of events and mean changes from baseline.

The statistical analyses will include all subjects who took at least one dose of randomized study medication. Subjects who discontinue the study will be assumed to be smokers for the remainder of the study. In computing the CQR, those subjects will be included in the denominator but not in the numerator. A logistic regression model will be fitted to compare the CQR and will include treatment as independent variables.

The proportion of participants from each study group who will be lost to follow-up, who will be abstinent will be computed from the 24 weeks follow-up data. Subjects who will not attend follow-up visits will be considered smokers. The student T-test will be used to compare between mean values of continuous variables in either intervention groups, while the Chi-square test will be used to compare difference between categorical variables. Multivariate logistic regression will be used to identify independent predictors associated with continuous abstinence.

## 2.9. Discontinuation criteria

This clinical study will be stopped when required study numbers are achieved. Recruitment at the centre may be stopped for reasons of particularly low recruitment, protocol violation, inadequate data recording. Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB and drug safety problems.

The reason for a subject discontinuing from the study will be



recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response. A discontinuation must be reported immediately to the clinical monitor or his/her designated representative if it is due to a serious adverse event. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition. Subjects who discontinue treatment may continue participation in the study. Subjects will be required to maintain the visit schedule and may be eligible to continue participation in the nontreatment phase of the study.

## 2.10. Ethics

University of Catania Institutional Review Board approved all research procedures and we will obtain written informed consent from all participants. This study must be conducted in compliance with Institutional Review Board/Independent Ethics Committee (IRB/IEC) and informed consent regulations. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants. This study will be conducted in general according to the Declaration of Helsinki and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct. The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness and obtain written informed consent prior to the subject entering the study (before initiation of protocol-specified procedures). The informed consent document must be agreed to by IRB/IEC and must be in compliance with ICH GCP and in accordance with local regulatory and legal requirements, in language readily understood by the subject. Each subject's original consent form, signed and dated by the subject or by the subject's legally acceptable representative, and a witness to the informed consent discussion, will be retained by the investigator.

## 2.11. Trial status

Recruitment of participants will start in June 2019 and enrolment is expected to be completed in December 2019. Results will be reported in 2020.

## 3. Discussion

Recent studies of e-cigarettes for smoking cessation concluded that nicotine e-cigarette help smokers quit long term [12–14]. The main objective of the present study is to evaluate the efficacy of the use of varenicline in smokers who use electronic cigarettes (single or dual users) willing to quit. The transition from traditional cigarette to electronic cigarette can represent a first step towards the definitive exit from cigarette addiction and the further passage could be represented by the need to stop using also the electronic cigarette. Through the implementation of this study it will be possible to observe changes at the biological, psychological and behavioural level, on subjects that benefit from the use of the varenicline plus counselling treatment.

We have described a randomized-controlled trial with a study sample, composed of 140 subjects that exclusively smoke electronic cigarette (single users) and 140 subjects that instead use both electronic cigarette and classic cigarette (dual users), that will be divided into two

arms in order to evaluate the effects that the association between varenicline and counselling or placebo and counselling have on the smoking/vaping behaviour. The varenicline and its use in terms of efficacy has been evaluated in several clinical studies that underlie the observation of changes in the smoking behaviour of classical cigarette smokers ( $\geq 10$  cigarettes a day) [5–7]. The analysis of the results of these studies have shown that abstinence from smoking has been determined by the use of this molecule and has been evidenced by the patient's self-test through a measurement of exhaled carbon monoxide ( $\text{CO} \leq 10$  ppm) at onsite visits [5–7]. There are currently no studies on the use of varenicline to facilitate stop smoking nicotine electronic cigarettes in regularly exclusive e-cigarette users (single users) but there is a recent study that enrolled 124 dual users interested in varenicline use to help them in order to obtain a complete smoking cessation [8]. Of these 124 participants, 80 used varenicline and obtained the following abstinence rates at the 24-week follow-up, report: abstinence from smoking 17.5%, vaping 12.5%, both smoking and vaping 8.8%.

There are challenges associated with a study of this nature. The timing and nature of our study present unique challenges to recruitment. We discussed this study with different e-cigarettes consumer associations and they acknowledge that e-cigarettes usage is the first important time for smokers toward the smoking end game and they enthusiastically supported the idea of providing help for trial recruitment. Our primary aim on efficacy, rather than safety, is in direct response to the presence of several specific studies about varenicline delivered for 12 weeks. Intervention adherence is another challenge in this study, as the ability to adapt to each participant's individual situation, needs, and personality traits are critical to developing therapeutic alliance and engaging in a smoking cessation oriented intervention. To address this, we will follow the published recommendations established by the smoking cessation counselling derived by Standard Treatment Programme [15].

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2019.100412>.

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