Outline Study Protocol

Title	Effectiveness of digital recommendations for cytisine and varenicline on medication use and smoking cessation in adults using a smoking cessation app: protocol for a randomised controlled trial.
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Rationale	Smoking remains the leading cause of preventable illness and premature death in the UK (1) and is the single largest driver of health inequalities (2). Despite the proven effectiveness of structured behavioural support and pharmacotherapy (3-5), many smokers do not use these interventions, making long-term abstinence difficult to achieve (6, 7). Among available pharmacotherapies, varenicline is one of the most effective stop smoking medications (8), while cytisine, a plant-derived alkaloid with a similar mechanism of action to varenicline (9), has shown promise as a clinically effective, cost-effective and well-tolerated alternative (8, 10). The growing popularity of digital health interventions, particularly mobile apps (6, 11), has created new opportunities for delivering smoking cessation support. This study aims to assess the effectiveness of digital recommendations for cytisine and varenicline on smoking cessation medication use and their impact on increasing quit rates. Varenicline is a selective nicotinic acetylcholine receptor partial agonist that is effective in reducing cravings and blocking the rewarding effects of nicotine (8). However, there has been consistently low uptake possibly due to concerns regarding potential adverse effects, including nausea and abnormal dreams, which has prompted interest in alternative treatments (8). Cytisine, a plant-derived alkaloid, operates through a similar mechanism as varenicline, mimicking nicotine's effects to alleviate withdrawal symptoms (9). Cytisine has been used as a smoking cessation aid in Eastern and Central European countries for over 50 years and was recently introduced in the UK on prescription in January 2024 (12). Cytisine has been found to be as effective as varenicline, with some evidence suggesting it may offer a more favourable safety profile (8). Notably, cytisine is associated with fewer reported adverse effects making it a potentially attractive alternative for individuals seeking pharmacological support to quit smoking (13). Despite promising results, only limited research has directly compared cytisine with varenicline (e.g., (14)), particularly in the context of digital interventions and in the UK. The Smoke Free app (https://smokefreeapp.com/) is a widely used digital smoking cessation tool, with over 7.6 million downloads and around 60,000

	new users each month, that provides users with personalised quit plans, behavioural support, progress tracking, and pharmacotherapy recommendations (15). Digital platforms like Smoke Free offer an accessible and cost-effective means of delivering smoking cessation interventions (16, 17), overcoming common barriers such as time constraints and financial limitations associated with traditional support services (18). This study will leverage the Smoke Free app to conduct a randomised controlled trial (RCT), assigning participants to receive a digital recommendation for either cytisine or varenicline. By examining the effectiveness of these recommendations in a real-world digital setting, the trial will provide valuable insights into whether cytisine's natural plant-based appeal and potentially lower adverse-event profile translate to higher medication usage compared to varenicline, which could lead to higher overall quit rates given similar efficacy (8). In the context of the increasing use of digital health interventions, this study has the potential to inform future public health strategies aimed at reducing smoking prevalence through innovative, scalable, and cost-effective solutions.
Research questions	The primary research questions are: 1. Does a digital recommendation for cytisine or varenicline (intervention arms) compared to no recommendation (control arm) increase medication use (defined as percentage of participants in the intervention arms who use either varenicline or cytisine) at two months after enrolment among individuals using a stop smoking cessation app during their quit attempt? 2. Among participants who receive a digital medication recommendation, is there a difference in medication use between those recommended cytisine and those recommended varenicline at two months after enrolment? We will also address the following secondary research questions: How effective is the intervention (advice to use either cytisine or varenicline) in promoting: (i) Continuous abstinence over the past month, assessed two months after enrolment? (ii) Biochemically verified continuous smoking abstinence for the past six months, assessed seven months after enrolment by a) group allocation (cytisine vs varenicline vs control) and b) by use of recommended medication among those in the intervention arms?
Methods	
Study design	This will be a three-arm individually randomised controlled effectiveness trial.
Participants	Participants will be adult smokers residing in the UK who have downloaded and signed up to the Smoke Free app within the past week during the recruitment period. They must be intending to quit smoking in the next month, willing to participate in a 7-month study, be able to provide consent and meet all of the inclusion criteria and none of the exclusion criteria. Inclusion criteria are:

	(i) aged between 18 and 65 years old (as cytisine is available for prescription in UK to adults 18-65 years old), (ii) able to consent, (iii) residing in UK, (iv) English speaking, (v) current cigarette smoker, (vi) willing to be followed up by email and complete online questionnaires after two and seven months, (vii) interested in making a quit attempt within the next month, (viii) have downloaded and signed up to the Smoke Free app within the past week during the recruitment period and have set a quit date no more than 30 days in the future. Exclusion criteria are: (i) current enrolment in another smoking cessation programme/study, (ii) current use of smoking cessation medication, (iii) varenicline and/or cytisine use in the previous 12 months, (iv) pregnant/breastfeeding/planning to get pregnant, (v) self-reported moderate/severe renal impairment, (vi) treatment for active/latent tuberculosis, (vii) experience of a heart attack, stroke or severe angina within the previous two weeks, (viii) uncontrolled high blood pressure (> 150 mmHg systolic, > 100 mmHg diastolic), (ix) history of seizures. Eligibility will be assessed via screening questions embedded in the baseline questionnaire. Those who do not meet the inclusion criteria will be provided with information about the best ways to stop smoking (6).
Sample size	Power calculations were conducted using the *pwr* package in R. Assuming that 10% of participants in the control arm will report using a prescription smoking cessation medication (based on Smoking Toolkit Study data)(19) at 2-month follow-up, and that a digital recommendation will increase this to 16.8% (relative risk = 1.68), we estimate that at least 876 participants providing data on the primary outcome (i.e., reporting medication use or non-use at 2-month follow-up) would be required to detect this difference with 80% power, using a two-sided alpha of 0.05. This corresponds to 292 participants per arm in the 1:1:1 randomised trial, which is equivalent to a 2:1 ratio of participants receiving any medication recommendation (cytisine or varenicline) versus no recommendation (control). Using these same sample sizes of primary outcome completers, we also estimated the minimum detectable effect size for the secondary comparison of medication use between the cytisine and varenicline recommendation arms. Assuming a 16.8% average medication use rate across the two groups and setting alpha to 0.05, the smallest detectable relative risk with 80% power is approximately 1.69 with 292 participants per group. These correspond to medication use rates of approximately 21.1% in the cytisine

	arm and 12.5% in the varenicline arm, an absolute difference of 8.6 percentage points. Recruitment will continue until at least this number of participants have provided data on the primary outcome (medication use at 2-month follow-up), in order to ensure adequate power for the primary analysis. Power to detect analogous effects on secondary smoking cessation outcomes will be lower due to loss to follow-up and expected low rates of quitting.
Recruitment	Participants will be recruited through the Smoke Free app. Participants will self-enrol into the study using a link that they will receive when they sign up to Smoke Free app (both to the free and premium version of the app) and will complete a web-based screening questionnaire, which assesses the inclusion and exclusion criteria. Participants will be informed that the study involves completing an initial online questionnaire (baseline questionnaire) and further online questionnaires two and seven months later (follow-up questionnaires).
Compensation	Participants will be informed at baseline that they will receive a £10 gift voucher upon completion of the 2-month follow-up, with an additional £5 if they complete it within 24 hours. They will also receive a £5 gift voucher upon completion of the 7-month follow-up. Participants who report abstinence at 7-month follow-up will be offered another £5 gift voucher along with a carbon monoxide (CO) monitor for biochemical verification of their abstinence.
Randomisation	Those who are eligible and consent to participate in the trial will be randomised after completing the baseline questionnaire. Randomisation will be 1:1:1 at individual level with no restrictions (i.e., no blocking) and will be generated by an online automated algorithm, which counts to ensure each intervention will be displayed equally.
Blinding	Participants cannot be masked to treatment allocation. The investigators will be blinded to participants' treatment allocation until all data have been collected. The trial statistician will have no contact with participants throughout the trial and will remain blinded for the analysis.
Intervention	Control No specific medication recommendation arm Participants in this group will be advised to access the Smoke Free app using a unique link provided to participants in the no specific recommendation medication arm, where they will receive routine smoking cessation behavioural support during their quit attempt. One day after randomisation, they will receive an email to remind them to use the Smoke Free app for smoking cessation behavioural support. The Smoke Free app is a theory-driven and evidence-based smoking cessation app (15). The app is designed to support users through the first three months of their quit attempt by reinforcing motivation, tracking progress, and highlighting the benefits of a smoke-free lifestyle. It incorporates a range of behaviour change techniques, including goal setting, reward systems, trigger identification, and coping strategies, to help users manage cravings and sustain abstinence (15).

	Interventions Varenicline arm Participants in the varenicline arm will receive a digital recommendation and support to use varenicline during their quit attempt, along with information on varenicline's benefits and potential side-effects, instructions for proper use, and guidance on how to obtain the medication either free of charge or with the standard NHS prescription charge. They will also be advised to access the Smoke Free app using a unique link provided to participants in the varenicline arm, where they will receive smoking cessation behavioural support and advice on the benefits of using varenicline during their quit attempt. One day after randomisation, they will receive an email with similar information on varenicline's benefits and potential side-effects, instructions for proper use and guidance for obtaining the medication and a reminder to use the Smoke Free app for smoking cessation behavioural support. Cytisine arm Participants in the cytisine arm will receive a similar digital recommendation to use cytisine during their quit attempt, along with information on its benefits and potential side-effects, instructions for proper use and guidance on obtaining the medication either free of charge or with the standard NHS prescription charge. They will also be advised to access the Smoke Free app using a unique link provided to participants in the cytisine arm, where they will receive smoking cessation behavioural support and advice on the benefits of using cytisine during their quit attempt. One day after randomisation, they will receive an email with similar information on cytisine's benefits and potential side-effects, instructions for proper use and guidance for obtaining the medication and a reminder to use the Smoke Free app for smoking cessation behavioural support. The Smoke Free app will be restricted for participants who enrol in the study, and they will only be able to access it through the unique link based on their group allocation. If participants opt out of the study, they will regain normal access to the Smoke Free app.
Measures	
Outcomes	The primary outcome will be percentage of participants reporting medication use (varenicline or cytisine use) at the 2-month follow-up. We will also report percentage of participants reporting varenicline or cytisine use among those recommended one of them at the 2-month follow-up. Secondary outcomes will be percentage of participants reporting: (i) continuous abstinence for one month assessed at 2-month follow-up. (ii) biochemically-verified continuous smoking abstinence for six months assessed at the 7-month follow-up by a) group allocation (cytisine vs varenicline vs control) and b) by use of recommended medication among those in the intervention arms. Following the Russell Standard, self-reported abstinence will be measured as not having smoked more than five cigarettes for the entire 6-month period preceding the 7-month follow-up (20). Analyses will follow the intention-to-treat principle. This means that all

	participants will be analysed in the groups to which they were originally assigned, regardless of whether they completed the study or adhered to the intervention. Multiple imputation will be used to account for missing outcome data (i.e., participants who will be lost to follow-up or did not provide outcome data). As a sensitivity analysis, missing data will be treated as no medication users (for medication use outcomes) and smokers (for smoking cessation outcomes) in the analysis. Self-reported abstinence will be biochemically verified by measuring participants' CO levels via a video call with a researcher. A CO monitor will be sent to participants who self-report abstinence at 7-month follow-up and those with a CO reading of less than 8 parts per million will be classified as abstinent (21, 22).
Baseline	The baseline questionnaire will assess the following: Participants' contact details: e-mail address, mobile phone number. Sociodemographic characteristics: age, sex (male, female, other), education (any versus no post-16 qualifications), financial status (live comfortably, meet needs with little left, just meet basic expenses, do not meet basic expenses (23)), country of residence (England, Scotland, Wales, Northern Ireland), ethnicity (Asian or Asian British background, Black, Black British, Caribbean or African background, White background, mixed or multiple ethnic groups (e.g., White and Black African or White and Asian), other ethnic group). Smoking related characteristics: number of cigarettes smoked per day, cigarette addiction (first cigarette within 5, 6-30, 31-60 or >60 minutes of waking), urges to smoke (How much of the time have you felt the urge to smoke a cigarette in the past 24 hours? (not at all, a little of the time, some of the time, a lot of the time, almost all the time, all the time); How strong have the urges been? (no urges, slight, moderate, strong, very strong, extremely strong)(24, 25), history of serious quit attempts (never, yes-not in the past year, yes-in the past year), past and current use of support for smoking cessation (prescription nicotine replacement therapy (NRT), NRT bought over the counter, varenicline, bupropion, cytisine, e-cigarettes, face-to-face behavioural support, telephone support, written self-help materials, website, apps, none, other).
Procedure	Participants will be assessed at enrolment (baseline), two months and seven months after enrolment. Table 1 summarises the schedule of enrolment and follow-up assessments for trial participants. Potential participants will have downloaded the Smoke Free app within the past week during the recruitment period and only those residing in the UK will see an on-screen message with information about the study and a link to access the baseline questionnaire via a weblink. Those who meet the

	eligibility criteria, assessed via the questionnaire and complete the baseline survey, will be automatically randomised to the intervention or control arms. All questionnaires will be conducted online via REDCap. Follow-up questionnaires will involve initial contact via email with a link to an online survey. Embedded links will provide the option of responding to the outcome measure assessed in that survey (at 2-month follow-up, medication use; at 7-month follow-up, 6-month continuous abstinence) in a single click. Three attempts will be made one day apart for each follow-up. Follow-up will be attempted at all follow-up points regardless of success at a previous point. A mailing system will be used for the e-mails to enable assessment of whether the e-mail will be (a) delivered versus hard bounce (i.e. permanent delivery problem) versus soft bounce (i.e., temporary delivery problem) and (b) opened. Invitations and contacts will be structured according to evidence-based methods for maximisation of response rate (26, 27). All invitations will mention incentives for responding. In order to boost the response rate for the 2-month and 7-month follow-ups, participants who provide their phone number in the baseline questionnaire and consent to receiving text messages and phone calls, will receive first a text message and then a phone call asking them to reply yes or no in order to record their response to the outcomes; medication use at 2-month follow-up and 6-month continuous abstinence at 7-month follow-up. Participants who report 6-month continuous abstinence at the 7-month follow-up will be asked to measure their CO levels to verify their abstinence. This will be conducted via a video call with a researcher, using a CO monitor provided by the study team. Debriefing will involve an e-mail sent after immediate completion of the final follow-up. It will thank participants for their help with the study and provide them with a contact e-mail for further information.
Withdrawal of participants	Participants will be informed that they may withdraw from the study at any time without giving a reason. Unless they withdraw consent, they will be followed up irrespective of smoking outcome or protocol violation. On the basis of the intention-to-treat principle, those who do not respond to end-point follow-up attempts will be retained in the analyses. Their outcomes will be imputed using multiple imputation (and classified as non-medication users and continuing smokers in a sensitivity analysis). Participants who indicate that they no longer wish to take part in the study will be excluded from the analyses.
Analyses	**Primary analyses: Medication use** The primary two comparisons will be as follows:

1. Any versus no specific medication recommendation: The first primary analysis will compare the combined medication recommendation arms (varenicline and cytisine) to the control arm (no specific medication recommendation). This analysis will assess whether recommending any medication (varenicline or cytisine) increases medication use.

2. Cytisine versus Varenicline recommendation: The second primary analysis will compare the cytisine recommendation arm to the varenicline recommendation arm among participants randomised to receive a medication recommendation. This analysis will determine if there is a difference in medication use between the two recommended medications.

Logistic regression will be used to model the binary outcome of medication use (yes/no), adjusting for covariates (sociodemographic and smoking-related characteristics at baseline). P-values will be calculated using Wald's test.

The models will include the treatment arms as predictors. To obtain marginal risk ratios (RR) and risk differences (RD) alongside 95% confidence intervals, we will use the *marginaleffects* package in R.

To account for missing outcome and covariate data, we will use multiple imputation with chained equations (in *mice* package). Imputation models will include experimental group, covariates, self-reported abstinence, and biochemically-validated abstinence. We will assume data are missing at random (MAR), meaning that having missing data on a variable does not depend on the true value of the variable, after accounting for predictor variables included in the imputation model. If less than 10% of data are missing, we will create 5 sets of imputations; otherwise, we will create 20 sets of imputations. Each set will be analysed separately and estimates combined using Rubin's rule.

Secondary analysis: Smoking abstinence outcomes

Above analyses will be repeated for smoking cessation outcomes, defined above in the measures section. As with the primary outcome, multiple imputation using chained equations (the *mice* package in R) will be used to account for missing outcome and covariate data.

Smoking cessation data are often missing not at random, as people who relapse to smoking are generally less likely to complete follow-up. However, the usual way to account for missing not at random, assuming "missing=smoking" (where all individuals with missing follow-up data are assumed to have relapsed to smoking), has been shown to be too extreme in internet-based smoking cessation trials (28). Instead, sensitivity analyses will examine the degree to which violations in the MAR assumption affect results. Multiple imputation with delta-adjustment will be used, with the degree of adjustment ranging from none (delta=0; MAR analysis) to very large (delta=100, approximating the missing=smoking assumption).

	Simple unadjusted complete case and "missing=smoking" analyses will be included in supplementary files as these are often used in meta-analysis. **Cost effectiveness** First, we will use the smoking cessation outcome directly observed in this trial—comparing the proportion of participants who report having quit smoking across trial arms at follow-up. This will provide a trial-based estimate of the intervention's impact on quitting, which can be used to estimate the potential health benefits (e.g., quality-adjusted life years [QALYs] gained) associated with the intervention. Second, we will adopt an indirect approach, which combines the observed effect of the intervention on smoking cessation medication use in this trial with existing evidence from prior systematic reviews on the effectiveness of cytisine and varenicline for supporting smoking cessation (8). This will allow us to estimate the potential impact of the intervention on smoking cessation outcomes under the assumption that its primary mechanism of action is through increased medication use. In both approaches, we will estimate the potential QALYs gained per user of the intervention, using a look-up table for QALYs associated with smoking cessation (29). These will be compared to the estimated cost of delivering the intervention to assess its cost-effectiveness. The intervention will be considered cost-effective if the cost per user does not exceed the value of the QALYs gained, using accepted UK cost-effectiveness thresholds(30).
Discussion	This is going to be the first RCT conducted in UK involving cytisine.
Governance and ethics	Ethical approval for the trial was obtained from the UCL Research Ethics Committee (1248).
Finance	The study is funded by Cancer Research UK (PRCRPG-Nov21\100002). VB and JB are members of the Behavioural Research UK Leadership Hub which is supported by the Economic and Social Research Council under grant (ES/Y001044/1).
References	1. Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. British Journal of Cancer. 2018;118(8):1130-41. 2. Office for Health Improvements & Disparities. Smoking Profile - Smoking and inequalities. In: Disparities OfHI, editor. 2023. 3. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;2013(5):Cd009329. 4. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. Cochrane Database Syst Rev. 2018;5(5):Cd000146.

5. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev. 2012;10:Cd008286.
6. Jackson SE, Brown J, Buss V, Shahab L. Prevalence of Popular Smoking Cessation Aids in England and Associations With Quit Success. JAMA Network Open. 2025;8(1):e2454962-e.
7. Hughes JR, Peters EN, Naud S. Relapse to smoking after 1 year of abstinence: a meta-analysis. Addict Behav. 2008;33(12):1516-20.
8. Lindson N, Theodoulou A, Ordóñez-Mena J, Fanshawe T, Livingstone-Banks J, Hajizadeh A, et al. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. Cochrane Database Syst Rev. 2023;9(9).
9. Rigotti NA. Cytisine--a tobacco treatment hiding in plain sight. N Engl J Med. 2014;371(25):2429-30.
10. De Santi O, Orellana M, Di Niro CA, Greco V. Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: A systematic review and meta-analysis. Addiction. 2024;119(4):649-63.
11. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y, Dobson R. Mobile phone text messaging and app-based interventions for smoking cessation. Cochrane Database of Systematic Reviews. 2019(10).
12. NHS. NHS rolls out 'stop-smoking' pill to help tens of thousands quit 2024 [Available from: https://www.england.nhs.uk/2024/11/nhs-rolls-out-stop-smoking-pill-to-help-tens-of-thousands-quit/.
13. Courtney RJ, McRobbie H, Tutka P, Weaver NA, Petrie D, Mendelsohn CP, et al. Effect of Cytisine vs Varenicline on Smoking Cessation: A Randomized Clinical Trial. JAMA. 2021;326(1):56-64.
14. Walker N, Smith B, Barnes J, Verbiest M, Parag V, Pokhrel S, et al. Cytisine versus varenicline for smoking cessation in New Zealand indigenous Māori: a randomized controlled trial. Addiction. 2021;116(10):2847-58.
15. Crane D, Ubhi HK, Brown J, West R. Relative effectiveness of a full versus reduced version of the 'Smoke Free' mobile application for smoking cessation: an exploratory randomised controlled trial. F1000Res. 2018;7:1524.
16. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev. 2016;4(4):Cd006611.
17. Taylor GMJ, Dalili MN, Semwal M, Civljak M, Sheikh A, Car J. Internet-based interventions for smoking cessation. Cochrane Database Syst Rev. 2017;9(9):Cd007078.
18. Kale D, Gilbert H, Sutton S. An exploration of the barriers to attendance at the English Stop Smoking Services. Addictive Behaviors Reports. 2019;9:100141.
19. Buss VE, West R, Kock L, Kale D, Brown J. Smoking Toolkit Study. Support used in quit attempts. Med Rx 2025 [Available from: https://smokinginengland.info/graphs/monthly-tracking-kpi.
20. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005;100(3):299-303.

21. Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res. 2020;22(7):1086-97.
22. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Smith KM, Bisal N, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. New England Journal of Medicine. 2019;380(7):629-37.
23. Williams VF, Smith AA, Villanti AC, Rath JM, Hair EC, Cantrell J, et al. Validity of a Subjective Financial Situation Measure to Assess Socioeconomic Status in US Young Adults. J Public Health Manag Pract. 2017;23(5):487-95.
24. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology (Berl). 2004;177(1-2):195-9.
25. West R, Ussher M, Evans M, Rashid M. Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. Psychopharmacology (Berl). 2006;184(3-4):619-27.
26. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet. 2011;378(9785):49-55.
27. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, Kwan I. Increasing response rates to postal questionnaires: systematic review. Bmj. 2002;324(7347):1183.
28. Jackson D, Mason D, White IR, Sutton S. An exploration of the missing data mechanism in an Internet based smoking cessation trial. BMC Med Res Methodol. 2012;12:157.
29. Stapleton JA, West R. A Direct Method and ICER Tables for the Estimation of the Cost-Effectiveness of Smoking Cessation Interventions in General Populations: Application to a New Cytisine Trial and Other Examples. Nicotine & Tobacco Research. 2012;14(4):463-71.
30. NICE. NICE cost impact statement: QOF indicator for smoking.; 2011.

Table 1. Schedule of enrolment, interventions and assessments

		Study period		
	Identification	Allocation	Follow-up	
Activities	Baseline	0	2-month	7-month
Enrolment				
Eligibility screen	x			
Informed consent	x			
Allocation		x		
	Interventions			
Cytisine		x		
Varenicline		x		
Control		x		
	Assessments			
Socio-demographic characteristics		x		
Cigarette addiction		x		
Motivation to quit		x		
Numbers of cigarette smoked/day		x		
Urge to smoke		x	x	x
Past year/2 months/6 months quit attempts		x	x	x

Past/ current use of smoking cessation medication		x	x	x
Sustained abstinence			x	x
Medication use			x	
Medication uptake			x	
Breath sample				x
Smoke Free app use			x	x