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NORWICH CTU

CoSTED

Cessation of Smoking Trial in the Emergency Department

Statistical Analysis Plan (SAP)

Version 3.00

31.10.2023

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SAP REVISION HISTORY

Document Name	Version No.	Reason for Revision	Effective Date
NCTU_M_Tat_5_v2.1_StatisticalAnalysisPlan COSTED_finalised_v1.0	2.0	* inclusion of additional secondary outcome * amendment to specification of existing secondary outcome	21/03/2023
NCTU_M_Tat_5_v2.1_StatisticalAnalysisPlan COSTED_finalised_v2.0_CLEAN	3.0	Addition of longer term follow up analysis plan – section 9.0	31/10/2023

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1.0 Administrative Information

Sponsor : Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH)

Sponsor Reference : 123-08-20

Funder : National Institute for Health Research – Health Technology Assessment

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Trial Registration : ClinicalTrial.gov: NCT04854616

Trial Identifier :

IRAS: 263674

Chief Investigator : Ian Pope / Caitlin Notley

Trial Statistician : Allan Clark

UKCRC Trials Unit : NCTU

Latest Protocol : 5.0

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2.0 Introduction

2.1 Background and Rationale

This is provided in section 4.1 of the protocol.

2.2 Objectives

The overall trial objectives are provided in section 4.2 of the protocol, however this SAP covers the following

1. To run an internal pilot, with clear stop/go criteria, primarily to test recruitment systems.
2. To definitively test real-world effectiveness of an ED based smoking cessation intervention in comparison with usual care, by comparing biochemically confirmed smoking abstinence at 6 month follow-up between trial groups.

3.0 Study Methods

3.1 Trial Design

A two-group, multi-centre, pragmatic, individually randomised, controlled trial with an internal pilot, and including economic evaluation and process evaluation.

Intervention: Opportunistic smoking cessation intervention comprising brief smoking cessation advice, the provision of an e-cigarette starter kit and training in its use and referral to stop smoking services (SSS). Following trial specific training up to 15 minutes of advice will be delivered by a smoking cessation advisor who will follow a protocol. Advice will address key aspects of the importance of quitting smoking, tailored to the patient where possible. Advice of up to 15 minutes will also be offered about how to use an e-cigarette efficiently to satisfy nicotine cravings, alongside the referral to local SSS.

Control: Usual care plus signposting to NHS smoking cessation services through provision of written information about local services.

3.2 Allocation

Randomisation to treatment arm will take place after consent and baseline data has been collected, including CO verification of smoking status. The randomisation scheme will be computer generated by the NCTU data manager using a blocked design. Randomisation will be at the individual participant level (1:1) stratified by ED department. The block sizes will be 2,4 and 6 randomly permuted.

3.3 Sample Size

This is provided in section 5.8 of the protocol but is repeated below.

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The sample size is based on an expected quit rate of 12.2% in the intervention group. This was used for the intervention rate based on a US trial of an Emergency Department smoking cessation intervention using a brief intervention, referral to smoking cessation services and nicotine replacement (Bernstein et al., 2015). A quit rate of 6.2% was used in the control group based on an average of 3 studies of unmotivated quitters who received either sign posting or no intervention (Hennrikus et al., 2010; McFall et al., 2010; Pieterse et al., 2001). This is broadly in keeping with the result of a recent Cochrane review of incentives which found a quit rate of 7.2% amongst controls (Notley et al., 2019). A sample size using 90% power and the above expected quit rates gives a required sample size of 972 (486 per group) at the 5% level of significance using a two-tailed test. No increase for drop-out has been made as dropouts, individuals for whom we do not have the primary outcome data, will be assumed to have returned to smoking. This assumption is standard in the smoking cessation literature as the pattern of missingness is not random (West et al., 2005).

3.4 Framework

This is a superiority framework comparing the intervention to the control.

3.5 Timing of outcome assessments

The schedule of outcome assessments is given in section 5.7 of the protocol and is repeated below

	Screening	**Eligibility/ Baseline**	**Smoking advice**	**1 month follow up**	**3 month follow up**	**6 month follow up**	**LT follow up**
Type of contact	**Member of ED clinical care team**	**Member of the site research team**	**Site smoking cessation advisor**	**Text message**		**Link to online CRF or paper sent**	**Text message, e-mail or post**
Eligibility	X						
Participant Information	X						
Informed Consent		X					
Check eligibility		X				X	
Demographics		X					
Self-reported smoking		X		X	X	X	X
Quit attempts		X				X	
Time to relapse						X	
Cigarette & tobacco use		X				X	
Nicotine dependence		X				X	
Motivation to stop		X				X	
E-cigarette use		X				X	
Incidence of dry cough		X				X	
Incidence of mouth or		X				X	
Quality of life - EQ-5D-		X				X	
Self-reported use of		X				X	
Adverse events				X	X	X	

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Self-reported use of		X				X	
Randomisation		X					
Smoking Cessation			X				
Referral to smoking			X				
E-cigarette given			X				
Signposting to NHS			X				

3.6 Interim analyses and stopping guidance

There will be no formal interim analyses or stopping guidance. However, the trial does have progression criteria the end of the internal pilot stage after three months recruitment. These are listed below

Green: If, 3 Months after the start of recruitment **any** of the following criteria are met or exceeded then we expect the trial to recruit >972 (90% power) within the 12 months period.

1. Average monthly recruitment per site in Month 3 = 19

2. Monthly trial recruitment in Month 3 = 95

3. Cumulative randomisations by end of month 3 = 159

Amber: If 3 Months after the start of recruitment the **green** criteria above have not been met but the **amber** criteria below have been met then then the trial will be on course to only recruit to approximately 712 (80% power) within the 12 months period and would require approximately a 3 month extension to recruitment to reach 90% power.

1. Average monthly recruitment per site in Month 3 = 15

2. Monthly trial recruitment in Month 3 = 75

3. Cumulative randomisations by end of month 3 = 125

If recruitment levels are between amber and green, then an urgent TSC meeting will be convened to discuss strategies to improve site / participant recruitment and the possibility of opening additional sites. If improvements do not occur by Month 6 then the funder will be notified and the TSC will meet again to discuss whether any other changes to the project can be made or whether consideration of discontinuing the study should be made.

Red: If 3 Months after the start of recruitment none of the **amber** criteria above are met then it is unlikely that the trial will recruit enough participants for 80% power, even if a short extension to recruitment was provided. If this is the case the TSC will meet to discuss whether any other changes to the project can be made or whether consideration of discontinuing the study should be made.

3.7 Timing of analyses

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The internal pilot does not require the analysis of any outcomes or unblinded data so is not considered as 'analysis' for this SAP. The analysis will be done once the database is locked and the SAP approved once all of the outcome data has been collected.

4.0 Statistical Principles

4.1 Levels of statistical significance

A 5% level of significance and 95% confidence intervals will be used throughout.

4.2 Analysis populations

In this trial we have two populations

ITT population: the set of individuals who are randomised as the 'main' participant defined as the attending patient when eligibility criteria are met (regardless of whether or not the accompanying person wishes to participate and is eligible to do so), or the accompanying person if the attending patient is not eligible/does not wish to participate.) in the original randomised allocations.

ITT+ population: the set of individuals in the ITT population plus those who are participating as the 'accompanying' participant.

The analysis will be done separately on both of these populations.

4.3 Treatment Adherence

Compliance with the intervention will be reported as per the table below.

Table 4.3.1: Compliance

	Intervention delivery	
	ITT (N=)	ITT+ (N=)
Leaflet given, & 15 minute smoking cessation advice		
E-cigarette starter kit given, & advice on use		
Referral to smoking cessation services		

4.4 Protocol deviations

Protocol deviations will be discussed at the TMG and will be reported as a list. A decision will be made, blind to the intervention, of if the participant should be excluded from the analysis.

5.0 Trial Population

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5.1 Screening data

The following data and tables will be reported from the screening data.

Table 5.1.1: Screening data by month of approaching patient

Month of screening	Number of patients approached	Number interested in participating	Number eligible* (pre-screening)	Number giving consent	Number eligible **	Number randomised
Jan 2022						
Feb 2022						
Mar 2022						
Total						

* Pre-screening eligibility criteria: inclusion: >= 18, smokes at least one cigarette (or equivalent) per day, attending ED for medical treatment (or accompanying someone attending ED for medical treatment; exclusion criteria: requiring immediate medical treatment, in police custody, known history of allergy to nicotine replacement products, dual user, lacks capacity, has already participated in the trial (see table 3 for frequency of non-eligibility criteria)

** CO reading > 7ppm, (see table 5.2.2 for frequency of ineligible CO values)

Table 5.1.2: Reasons for declining

	Number (% Of those declining participation)	Percentage of those approached
Too busy		
Does not want to do research		
Not interested in e-cigs		
Feels too unwell		
Does not want to quit		
Not interested (in engaging)		
does not want to stay longer in ED		
Language barrier		
Left the department		
Mental health		
Already engaged with SSS or GP		
Wants to quit alone		
Just not the right time		
Dual user or not daily smoker or lacks capacity		
Unable to read the consent form		
Cannot do CO reading		
Would be unable to participate in follow-up		

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AP – patient not interested		
No reason given		

5.2 Eligibility

5.2.1 Participant Inclusion Criteria

1. Adult ≥ 18 years
2. Current daily tobacco smoker (self-reporting smoking of at least one cigarette per day).
3. Attending the ED for medical treatment (or accompanying a patient attending for medical treatment).
4. Submitting an expired carbon monoxide (CO) breath test reading of ≥8 parts per million (ppm).

5.2.2 Participant Exclusion Criteria

Requiring immediate medical treatment as defined by the treating clinician, therefore unavailable.
2. In police custody.
3. A known history of allergy to nicotine replacement products.
4. Currently defined as a dual user (already using an e-cigarette daily as well as smoking tobacco daily).
5. Without the capacity to give informed consent for participation in the study
6. Have taken part in the CoSTED trial already

This will be reported as below.

Table 5.2.1: Reasons for ineligibility

	Frequency (%) (N=)
Pre-screening eligibility criteria met	
Reason for exclusion (n=)	
b) Absence of inclusion criteria	
Aged 18 years or over	
Daily tobacco smoker, smoking at least one cigarette (or equivalent) per day	
Attending ED for medical treatment / accompanying someone attending for medical treatment	
Presence of exclusion criteria	
Requiring immediate medical treatment (defined by treating clinician), therefore unavailable	
In police custody	
A known history of allergy to nicotine replacement products	
Currently dual user – already using an e-cigarette daily as well as smoking tobacco daily	
Lacking capacity to give informed consent for participation in the study	
Has taken part in the trial already	

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Table 5.2.2: CO levels of those not achieving eligibility criteria of >7ppm

CO reading (ppm)	Frequency (%)
2	
3	
4	
5	
6	
7	
CO level missing*	

5.3 Recruitment and participant flow

Table 5.3.1: Participant accrual (e.g. per time period, cumulative, if appropriate against predicted accrual in graphical form) for main participants (ITT population only)

Month of recruitment	Predicted	Actual	Cumulative Predicted	Cumulative Actual
January 2022	9		9	
February 2022	55		64	
March 2022	95		159	
April 2022	136		295	
May 2022	136		431	
June 2022	136		567	
July 2022	136		703	
August 2022	136		839	
September 2022	136		975	

Graph of predicted vs actual recruitment

A CONSORT diagram will also be produced.

5.4 Withdrawal information

Follow-up rates and reasons for withdrawal will be reported in the following tables.

Table 5.4.1: Follow-up

	ITT population		ITT+ population	
	Control (n=)	Intervention (n=)	Control (n=)	Intervention (n=)
No response at 1 month n(%)				
No response at 3 months n(%)				
No response at 6 months n(%)				

Table 5.4.2: Reasons for loss to follow-up.

	ITT population		ITT+ population	
	Control (n=)	Intervention (n=)	Control (n=)	Intervention (n=)
Reason lost to follow-up (month 1)				
Reason 1, n(%)				
Reason 2, n(%)				
….				
Reason lost to follow-up (month 3)				
Reason 1, n(%)				
Reason 2, n(%)				
….				
Reason lost to follow-up (month 3)				
Reason 1, n(%)				
Reason 2, n(%)				
….				

5.5 Baseline participant characteristics

[List the baseline characteristics and how they will be summarized.]

The baseline characteristics will be summarized according to the table below.

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Table 5.51: Baseline characteristics of trial participants

	ITT population (n=)		ITT+ population (n=)	
	Control (n=)	Intervention (n=)	Control (n=)	Intervention (n=)
Age, mean (SD)				
Gender, n(%) Female Male				
Main participant "Accompanying" participant				
Ethnicity				
Deprivation				
Motivation to quit				
Site				
Norwich (01)				
Royal London (02)				
Homerton (03)				
Leicester (04)				
Edinburgh (05)				
Addenbrookes (06)				
Reason for attendance at A&E				
Chest Pain				
Shortness of Breath				
Abdominal Pain				
Injury (including laceration)				
Other medical issue				
Mental Health Issue				
Other				
Not asked (accompanying patient)				
Median (IQR) number of cigarettes per day				
Median (IQR) number of pipes full of tobacco per day				
Median (IQR) number of cigars, cheroots or cigarillos per day				
Median (IQR) number of water pipes per day				
Median expire carbon monoxide level ppm				
Employment Status				
Full time				
Self-employed / freelance				
Part time				

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Unemployed & looking for work				
Long-term unemployed or never worked				
Unable to work due to sickness of disability				
Full time carer (eg of children / other family)				
Retired				
Full time student				
Other				
Score on the Fagerstrom test for nicotinedependence* mean (SD) median (IQR)				
Use of nicotine replacement therapy in the past 3 months				
Use of e-cigarettes in the last 3 months				
Lives with other smokers				
Attendance at group session with someone from Smoking Cessation services in past 3 months?				
Attendance at one-to-one session with someone from Smoking Cessation services in past 3 months?				
Talked to GP (on phone or in person) in past 3 months?				
Stayed in hospital as a patient for more than 24 hours in past 3 months				

6.0 Analysis

The following sections are for the ITT population only, the extension to the ITT+ population is discussed in section 6.5

6.1 Outcome definitions

6.1.1 Primary Outcome

The primary outcome will be self-reported continuous smoking abstinence, biochemically validated by CO monitoring at 6 months with cut off of ≥8ppm (i.e. a reading of 7 or less will denote abstinence), according to the Russell standard (SRNT 2002, West et al., 2005; Raiff et al., 2010). Participants who self-report

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having quit smoking at 6 months will then have their report verified by a carbon monoxide (CO) breath test, undertaken, by a researcher at the hospital, their home, another location or by remote CO testing, to confirm cessation.

6.1.2 Secondary Outcomes

The secondary outcomes are

1. 7-day point prevalence abstinence (i.e. current smoking status, self-report of having smoked no cigarettes (not even a puff) in the past seven days, biochemically validated by carbon monoxide monitoring with cut off of ≥8 ppm)
2. Number of quit attempts
3. Time to relapse (if applicable)
4. number of cigarettes per day
5. Nicotine dependence (Heatherton et al. 1991). This a 6-item self-reported questionnaire. The total score is constructed by adding up the responses to each item. The score ranges from 0 to 10, with high values indicating more dependence.
6. Number of times using an e-cigarette per day
7. Frequency of e-cigarette use in past 6 months (daily/less than daily /none)
8. Incidence of self-reported dry cough in past week (yes/no) (Hajek et al, 2019)
9. Incidence of mouth or throat irritation
10. Motivation to Stop Smoking (Kotz et al, 2013) (single question)
11. Self-reported use of healthcare services in the last 6 months
12. Self-reported use of smoking cessation services in last 6 months
13. Quality of life (using the EQ-5D-5L) (EuroQol, 2019)

6.1.3 Tertiary outcomes

None.

6.2 Analysis Methods

6.2.1 Primary outcome

The primary outcome will be compared between treatment groups using a log-binomial regression adjusting for site. This will allow the estimation of the relative risk of abstinence between the two treatment groups. The risk difference will be estimated from this model using the predicted risk, those factors in the model which are categorical will be set at the value with the largest number of participants and the continuous factors will be set at the mean value. Any individual with missing data will be assumed to have relapsed, in the event of the abstinence not being able to be confirmed biochemically it will also be assumed that the person has relapsed.

Table 6.2.1: Summary for primary outcome (will be reported for the ITT and ITT+ populations)

	ITT population	Minimally adjusted	Fully adjusted

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Outcome	Control (n=)	Intervention (n=)	Relative risk (95% CI)	p-value	Difference in risk (95%CI)	Relative risk (95% CI)	p-value	Difference in risk (95%CI)
Self-reported continuous smoking abstinence at 6 months, biochemically validated (CO reading of 7 or less),n(%)								
Self-reported continuous smoking abstinence at 6 months, n(%)								

6.2.2 Secondary outcomes

Binary outcomes

The following binary outcomes

1. Seven-day point prevalence of abstinence;
2. Incidence of mouth or throat irritation;
3. Incidence of dry cough.

Will be analysed in the same way as the primary outcome, that is they will be compared between treatment groups using a log-binomial regression adjusting for site. This will allow the estimation of the relative risk of abstinence between the two treatment groups. The risk difference will be estimated from this model using the predicted risk, those factors in the model which are categorical will be set at the value with the largest number of participants and the continuous factors will be set at the mean value. For the seven-day point prevalence of abstinence missing values will be assumed to be relapsed.

Continuous outcomes

The following continuous outcomes

1. Number of quit attempts;
2. Number of cigarettes per day;
3. Number of times using an e-cigarette per day;
4. Nicotine dependence;

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These will be summarized using the mean and standard deviation in each group and compared between treatment groups using a linear regression adjusting for site. This will allow the estimation of the mean difference between the two treatment groups. In the, hopefully, likely event that the first three have small means then a Poisson regression, or Negative binomial regression model will be used. This model will still adjust for site and report ratio of the mean between the two groups.

A sensitivity analysis of the number of times using an e-cigarette per day will be conducted by truncating the responses to have a maximum value of 30. This analysis will be undertaken using a Mann-Whitney test.

Ordinal outcomes

Motivation to stop smoking and frequency of e-cig use in past 6 months will be summarized using the percentage in each response category. It will be compared between groups using a Mann-Whitney test.

Time-to-event outcomes

The time to relapse will be summarized as the median (IQR) in each group and displayed graphically using a Kaplan-Meier Plot. It will be formally compared using a Cox-proportional hazard regression model adjusting for site and will report the hazard ratio between the two groups. The assumptions of the proportional hazard model will be checked using Schoenfeld residuals and if appropriate adjustments, such as time stratification, cannot be found then a Royston-Parmar model will be (Royston, Parmar 2001)

Table 17: Secondary efficacy outcomes

	ITT population		Minimally adjusted		Fully adjusted	
Outcome	Control (n=)	Intervention (n=)	Effect size (95%CI)	p-value	Effect size (95%CI)	p-value
7-day point prevalence abstinence at 6 months						
Number of quit attempts at 6 months						
Time to relapse (if applicable) at 6 months						
Number of cigarettes per day at 6 months						

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Nicotine dependence at 6 months						
Number of times using an e-cigarette per day at 6 months						
Incidence of self-reported dry cough at 6 months						
Frequency of e-cigarette use in past 6 months						
Incidence of throat and/or mouth irritation in past week, at 6 months						
Carbon monoxide concentration for those who report smoking cessation						
Motivation to Stop Smoking: I don't want to stop smoking I think I should stop smoking but don't really want to I want to stop smoking but haven't thought about when I REALLY want to stop smoking but I don't know when I will I want to stop smoking and hope to soon						

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I REALLY want to stop smoking and intend to in the next 3 months I REALLY want to stop smoking and intend to in the next month						
Self reported smoking status at 1 month follow-up: Has smoked in past 7 days						
Self reported smoking status at 3 month follow-up: Has smoked in past 7 days						

6.3 Missing Data

As mentioned in the above our primary analysis will replace missing abstinence values with relapse and the analysis of the other endpoints will be of available case. A sensitivity analysis will be conducted using multiple imputation assuming that the data are not missing at random. Alternative assumptions will be investigated but it will not be known which approaches/assumption are appropriate until we have more data about the missingness pattern. However, a reasonable NMAR choice would be to assume that those with missing data have worse outcome than those without missing data.

6.4 Additional analyses

6.4.1 ITT+ population analyses

The previously described analysis for the ITT population will be repeated for the ITT+ population. The analysis will be based on the same models, assumptions and missing data methods but the models will be extended to have random effects to account for the clustering. It is possible that this modelling may

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prove difficult or impossible if only a handful of additional participants are included in the ITT+ population, in this case the analysis will be repeated without adjusting for clustering.

6.4.2 Subgroup analyses

Subgroup analyses will be undertaken for the primary outcome and the 7-day abstinence outcome at 6 months for the following groups based on baseline characteristics in the ITT population:

- Ethnicity (white vs other)
- Motivation (cats 1-5 vs 6 & 7)
- Lives with other smokers (yes/no)
- Deprivation (split into tertiles)
- Nicotine dependence (1 -4 (low), 5-7 (moderate), 8+ (high))
- Previous use of an e-cigarette in the last 3 months (yes/no)
- Patient/accompanying person

6.5 Safety analyses

Only descriptive analysis of the SAE and SE will be reported. These will simply be listed as per the tables below.

Table 6.5.1: serious adverse events

	Control (N =)		Intervention (N =)	
	Events	Individuals	Events	Individuals
Number (%) of serious adverse events				
Number (%) of serious adverse events related to intervention				

Table 6.5.2: adverse events

	Control (N =)		Intervention (N =)	
	Events	Individuals	Events	Individuals
Number (%) of adverse events				

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6.5 Software

Stata 17.1 or higher will be used for the majority of the analyses, however alternative software may be used if required.

7.0 Changes post sign off

Change	Justification
The analysis of the ITT+ population was changed from using random effects modelling to using the same models as the ITT population. This ignores the clustering present in the data.	The ITT+ population was largely the same as the ITT population and to be judge the effects of adding the extra participants it was felt that using the same models would the comparison more direct.
The model used for the primary outcome to estimate the risk difference was a log-binomial model with an identity link.	This was changed as it was felt that this would be easier to interpret.

9.0 Additional analyses (post original SAP sign-off)

The following analyses will be done on the ITT and ITT+ populations separately.

In addition to the original outcome measures, listed above, longer term data on self-reported abstinence was subsequently obtained on individuals who provided consent. In order to include all participants in this analysis, the following assumptions will be made:

- Individuals who did not provide consent to be contacted will have the outcome set at the value of the six-month outcome along with the time since randomization set to 6 months;
- Individuals who did provide consent to be contacted but did not respond will be assumed to have returned to smoking along with the time since randomization set to 12 months;
- Individuals who did provide consent to be contacted and did respond will have their response set to the response and the time since randomization set to the number of whole months since randomization.

This outcome will be compared between treatment groups using a log-binomial regression adjusting for site and time since randomization in months. This will allow the estimation of the relative risk of abstinence between the two treatment groups. An additional model using a binomial regression with an identity link adjusting for site and time since randomization in months. This will allow the estimation of the risk difference of abstinence between the two treatment groups.

In addition to the above we will also

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1. A repeat of the baseline table for individual who gave consent for long-term follow-up only;
2. A comparison of the baseline characteristics of individuals who gave consent to those who did not give consent for long-term follow-up;
3. A comparison of the smoking outcomes at 6 months of individuals who gave consent to those who did not give consent for long-term follow-up;
4. A comparison of the intervention and control groups for those who did not give consent for long-term follow-up using a log-binomial regression adjusting for site and time since randomization in months. This will allow the estimation of the relative risk of abstinence between the two treatment groups. An additional model using a binomial regression with an identity link adjusting for site and time since randomization in months. This will allow the estimation of the risk difference of abstinence between the two treatment groups. Individuals who did not respond will be assumed to have relapsed.

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