CPIT III

The Smoking Cessation in Pregnancy Incentives Trial: A Phase III Randomised Controlled Trial

STATISTICAL ANALYSIS PLAN

Draft v1.0

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1 General

1.1 Document Scope

This statistical analysis plan (SAP) covers the reporting of the trial progress and planned effectiveness analyses of the CPIT III trial. Analyses relating to health economic or qualitative data or any further exploratory post-hoc analyses are not covered by this SAP.

1.2 Glossary

AE	Adverse event
BMI	Body mass index
CACE	Complier average causal effect
CI	Chief Investigator
CO	Chemical symbol for carbon monoxide
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
EDD	Estimated Date of Delivery
FTND	Fagerström Test for Nicotine Dependence
IMD	Index of Multiple Deprivation
LSOA	Lower-layer Super Output Areas
NHS	National Health Service
NRT	Nicotine replacement therapy
PIS	Patient information sheet
ppm	Parts per million
REC	Research Ethics Committee
SAE	Serious adverse event
SQD	Set quit date
SOP	Standard operating procedure
SSS	Stop Smoking Service(s)
TCC	Trial Contact Centre
TMG	Trial Management Group
TSC	Trial Steering Committee
YTU	York Trials Unit

1.3 Procedural Documentation

1.3.1 Standard Operating Procedures

The following YTU SOPs and guidance documents will apply to the conduct and documentation of the CPIT III trial analysis:

S01	Statistical Considerations	Latest version: 5.0
SG02	Statistical Reporting Guidance	Latest version: 3.0

1.3.2 Associated Documentation

Appropriate YTU standard forms apply. Any assumptions made during the processing and merging of data as well as for the analysis will be documented (internal document reference numbers in bracket) using a Trial Assumptions Form (F23). In the event of necessary changes or additions to analyses detailed here, these will be documented on a Statistical Analysis Plan Departure Form (F24). The statistical analysis will be signed off using a Primary Analysis Sign-off Form (F16) and Statistical Quality Assurance Checklist (C03).

2 Trial Summary

The following sections give a summary of the CPIT III trial. Full details are given in the Study Protocol (latest version 4.0, dated 11/03/2020) and the published trial protocol paper [1].

2.1 Objectives

2.1.1 Primary Objective

The primary objective was to assess whether offering financial incentives in addition to usual Stop Smoking Service (SSS) support to pregnant smokers was effective in increasing the smoking cessation rate at late pregnancy.

2.1.2 Secondary Objectives

The secondary objectives were:

- To compare quit rates at four weeks post quit date between women offered incentives and those receiving usual SSS care only
- To compare quit rates at six months after birth (point abstinence) and until six months after birth (continuous abstinence) between women offered incentives and those receiving usual SSS care only
- To assess the cost effectiveness of financial incentives
- To identify the effects of differences in SSS, maternity care and demographic diversity of pregnant smokers on the effectiveness, cost effectiveness and transferability of financial voucher incentives

2.2 Design

CPIT III is a phase III, pragmatic, multi-centre, randomised controlled trial of the offer of financial incentives added to usual SSS care to engage with SSS and quit smoking versus usual care alone. In addition, economic and process evaluations were embedded in the study.

2.3 Intervention

2.3.1 Original intervention

The intervention was composed of several stages, each of which involved the offer of a financial incentive in the form of a Love2shop gift voucher, delivered via registered post.

The first stage of the intervention was designed to encourage participants to engage with SSS, while the remaining stages were designed to encourage participants to quit smoking and remain abstinent.

At the first stage, if the participant attended an appointment with the SSS and set a date on which they would quit smoking, they received a gift voucher with a value of £50.

At the second stage, the smoking status of those participants who engaged with SSS and set a quit date was obtained from the SSS at four weeks post-quit date. Smoking status was ascertained by asking the participant the question:

1. Have you smoked (even a puff) in the last two weeks?

Participants who answered ‘No’ were contacted by a research nurse to arrange an appointment to obtain a Carbon Monoxide (CO) breath test reading, where this had not already been collected by the SSS. Participants who had a CO reading less than or equal to the accepted threshold for their site received a gift voucher with a value of £50. Table 1 gives details of the CO threshold for each site.

Table 1: CO threshold for each site

Site	CO threshold (<=ppm)
Lanarkshire	4
Belfast	3
Salisbury	4
Poole	4
Isle of Wight	5
Dorchester	4
Portsmouth	4

At the third stage, the smoking status of those participants, who met the criteria to receive a shopping voucher at the second stage, was obtained from the SSS (where available) or by a research nurse at 12-weeks post quit date. Smoking status was obtained by asking the participant the question:

1. Have you smoked at all since your one-month follow-up?

Participants who answered 'No' were contacted by a research nurse to arrange an appointment to provide a CO breath test reading, where this had not already been collected by the SSS. Participants who had a CO reading less than or equal to the accepted threshold for their site received a gift voucher with a value of £100.

At the fourth stage, participants were contacted by the trial team at a random date between 34 and 38 weeks gestation, regardless of whether or not they met the criteria for the previous shopping vouchers. The participants were asked the following questions:

1. Have you smoked at all in the last eight weeks?
2. If yes, have you smoked more than five cigarettes in total in the last 8 weeks?

If the participant answered 'No' to the first question, or 'Yes' to the first question and 'No' to the second question, they were contacted by a research nurse to arrange an appointment to obtain a CO reading. Participants who had a CO reading less than or equal to the accepted threshold for their site had to provide a saliva sample and once the saliva sample was collected/received, they were sent a gift voucher with a value of £200.

2.3.2 Changes to the intervention in response to the Covid-19 pandemic

Due to the Covid-19 pandemic, SSS were disrupted. As a result, on the 16th of March 2020 the following changes were made for the intervention group:

- Participants who received SSS behavioural support and set a quit date via telephone (where this would have previously been conducted face-to-face) were considered to have engaged with the SSS, and received a gift voucher with the value of £50.
- Participants who self-reported as having quit with no CO verification at the 4-week follow-up received a gift voucher with the value of £50.
- Participants who self-reported as having quit at the 4-week follow-up were contacted at the 12 week follow-up. If they self-reported as quit with no CO verification at the 12-week follow-up they were sent a gift voucher with the value of £100.
- Participants who self-reported as having quit at the primary outcome stage in late pregnancy and for whom a saliva sample was received by the trial team were sent a gift voucher with the value of £200.

2.4 Usual care

Stop smoking support is freely available to pregnant women throughout the UK. Models of support differ however depending on where women live. In general, two main types of support are offered which can be described as 'specialist' (just for pregnant women) or 'generic' (for all smokers including pregnant women). Within this framework, support offered commonly includes: (1) individual/group support provided by specially trained advisers who may be nurses, or midwives, (2) support provided in hospital setting, women's homes or other mutually acceptable venue, (3) at least one face-to-face counselling session with follow-up support, often by telephone, to 12 weeks after a quit date is set, and (4) advice on use of NRT utilising various models of prescribing (e.g. nurse/GP prescribing/pharmacy).

The National Institute of Health and Care Excellence (NICE) - PH26 Smoking: stopping in pregnancy and after childbirth published comprehensive guidance in 2010 regarding services that should be provided to pregnant smokers (National Institute for Health and Care Excellence. Quitting smoking in pregnancy and following childbirth. 2010. https://www.nice.org.uk/guidance/ph26).

2.5 Outcomes

2.5.1 Primary Outcome

The primary outcome is cotinine/anabasine verified abstinence from smoking for at least 8 weeks towards the end of pregnancy. All participants were contacted by the Trial Team at a random date between 34 and 38 weeks gestation and asked the following questions:

1. Have you smoked at all in the last eight weeks?
2. If yes, have you smoked more than five cigarettes in total in the last 8 weeks?

If the participant answered 'No' to the first question, or 'Yes' to the first question and 'No' to the second question, they were contacted by a research nurse to arrange an appointment to biochemically verify their smoking status. Participants were asked to provide a CO reading and a saliva sample (or urine sample when saliva collection could not be tolerated), which was tested for cotinine in the first instance. Where the cotinine result was less than or equal to the threshold (Table 2) and the participant had not reported any NRT/e-cigarette use then the participant was defined as a biochemically verified non-smoker.

Participants who indicated current NRT/e-cigarette use and had a saliva cotinine result < 10ng/ml were defined as biochemically verified non-smokers. Where participants indicated current NRT/e-cigarette use and the saliva cotinine result was ≥ 10ng/ml, saliva samples were also tested for anabasine. Where the anabasine result was less than or equal to the threshold 0.2ng/ml and the saliva cotinine result was ≥ 10ng/ml then the participant was defined as a biochemically verified non-smoker.

Urine samples were also collected from participants who indicated NRT/e-cigarette to allow further assaying in the event of any dubiety. At present however there is no defined threshold for anabasine in urine and a judgement regarding smoking status would need to be taken by the Research team in conjunction with advice from ABS Labs in this scenario.

Table 2: Thresholds for cotinine samples in saliva

Cotinine threshold, ng/ml	
Saliva	10.0
Urine	50.0
Plasma	10.0

2.5.2 Secondary Outcomes

2.5.2.1 Engagement with SSS (Locally Defined) and Setting of Quit Date Before 26 weeks Gestation

A participant was defined to have engaged with SSS if they had attended an appointment with a smoking cessation advisor (face-to-face or by telephone) and agreed a quit date before reaching 26 weeks gestation (calculated using the estimated delivery date and the antenatal booking appointment date).

2.5.2.2 CO-validated abstinence from smoking for at least 14 days at four weeks after quit date

At the four-week stage, participants were asked the following question:

- Have you smoked (even a puff) in the last two weeks?

If the participant answered 'Yes' to this question, they were defined as a self-reported smoker at the four week time point, and if the participant answered 'No' they were defined as a self-reported non-smoker. Participants who provided a CO result less than or equal to the CO threshold for their site were defined as CO-validated non-smokers. Participants whose four-week follow-up was due after the 16th of March 2020 were not able to provide CO samples due to restrictions implemented in response to the Covid-19 pandemic.

2.5.2.3 Cotinine/anabasine verified self-reported point abstinence from smoking for at least 8 weeks at 6 months post-partum

At the 6 months post EDD stage, participants were asked the following question:

- Have you smoked at all in the past eight weeks?

If the participant answered 'No' to this question, they were defined as a self-reported non-smoker at the six months post EDD stage. If the participant answered 'Yes', they were asked a second question:

- Have you smoked more than five cigarettes in total in the last eight weeks?

If the participant answered 'No' to this question, they were defined as a self-reported non-smoker. If the participant answered 'Yes', they were defined as a self-reported smoker.

If a participant was defined as a self-reported non-smoker, they were asked to provide a CO reading, and a saliva/urine sample in order for their smoking status to be biochemically verified. The sample was tested for cotinine and a participant defined as a biochemically verified non-smoker where the result was less than or equal to the threshold (Table 2) and the participant had not reported any NRT/e-cigarette use.

Participants who indicated current NRT/e-cigarette use and had a saliva cotinine result < 10ng/ml were defined as biochemically verified non-smokers. Where participants indicated current NRT/e-cigarette use and the saliva cotinine result was ≥ 10ng/ml, saliva samples were also tested for anabasine. Where the anabasine result was less than or equal to the threshold 0.2ng/ml and the saliva cotinine result was ≥ 10ng/ml then the participant was defined as a biochemically verified non-smoker.

2.5.2.4 Cotinine/anabasine verified self-reported continuous abstinence from smoking from late pregnancy to 6 months post-partum

At the 6 months post EDD stage, participants were asked the following question:

- Have you smoked since your baby was born?

If the participant answered 'No' to this question, they were defined as a self-reported continuous non-smoker at the six months post EDD stage. If the participant answered 'Yes', they were asked a second question:

- Have you smoked more than five cigarettes in total since your baby was born?

If the participant answered 'No' to this question, they were defined as a self-reported continuous non-smoker. If the participant answered 'Yes' they were defined as a self-reported continuous smoker.

If a participant was defined as a self-reported non-smoker, they were asked to provide a CO reading, and a saliva/urine sample in order for their smoking status to be biochemically verified. The sample was tested for cotinine and a participant defined as a biochemically verified non-smoker where the result was less than or equal to the threshold (Table 2) and the participant had not reported any NRT/e-cigarette use.

Where participants indicated current NRT/e-cigarette use and the saliva cotinine result was >= 10ng/ml saliva samples were also tested for anabasine. Where the anabasine result was less than or equal to the threshold 0.2ng/ml then the participant was defined as a biochemically verified non-smoker.

2.5.2.5 Birth Weight

The weight of the baby in kilograms was collected to two decimal places. If the participant gave birth to more than one baby, the weight of the lightest baby was used.

2.5.3 Adverse events

Serious adverse events (SAEs) that are related to the intervention will be documented. It is not anticipated that the provision of shopping vouchers to women will be associated with any related SAEs.

2.5.4 Other Collected Data

- *Demographics:* Maternal age, height and weight, household income and ethnicity were collected at baseline.
- *Index of Multiple Deprivation (IMD) quintile:* The IMD is a measure that ranks each lower layer super output area (LSOA) in order of deprivation, with the most deprived LSOA being ranked the highest. The IMD was derived for each participant by mapping to the participant's postcode. From the IMD the IMD quintile was then derived. A value of 1 represents the most deprived quintile, while 5 represents the least deprived. The postcode used to derive the IMD quintile was collected at baseline.
- *The Fagerström Test for Nicotine Dependence (FTND):* The FTND is used for assessing nicotine dependence. The test is composed of six questions, the scoring of which is detailed in Appendix 8.1. The FTND was collected at baseline.
- *Other smoking information:* The age at which the participant started smoking and whether the participant was currently living with someone who smokes were also collected at baseline, along with information on whether the participant used NRT and/or e-cigarettes.

- *Antenatal appointment information:* The date of the antenatal appointment and the CO reading taken as part of routine care (where available) were collected.
- *EQ-5D-5L:* The EQ-5D-5L was collected as a standardised measure of current health status developed by the EuroQol Group for clinical and economic appraisal. The EQ-5D-5L consists of five questions and a visual analogue scale, each assessing a different quality of life dimension (Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression). A weighted and population referenced summary index is derived and will be reported and analysed as part of the health economic analysis.
- *Other birth data:* Parity and the baby's birth date was collected as well as the status of baby at birth (live/stillbirth).
- *Neonatal stay:* For babies admitted to neonatal care, length of stay was recorded.
- *Miscarriage data:* Any known occurrence of miscarriage was collected throughout the study duration. The date the event became known to the trial team and date of miscarriage (where available) was collected.

2.6 Sample size

The aim was to recruit 940 participants to the trial (470 per arm). This gave 90% power to detect a doubling of the smoking cessation rate from 7% to 14%, allowing 15% loss to follow-up. The smoking cessation rate in the control group was derived from the smoking cessation rate found in the feasibility trial [2], and two other large trials of smoking cessation interventions in pregnant smokers [3, 4]. The smoking cessation rate in the intervention group was derived from the cessation rate in the feasibility trial, along with considerations of the effect size that would be considered clinically important.

2.7 Randomisation

Participants were allocated using a 1:1 allocation ratio to either intervention or control using random permuted blocks with randomly varying block sizes. No stratification factors were used when randomising the participants.

To try to prevent participants in the incentives arm using the timing of the primary outcome to 'game' the study and falsely obtain the final incentives voucher, all participants were randomly assigned a date for primary outcome follow-up between 34 and 38 weeks gestation, which was calculated using the participant's EDD.

2.8 Blinding

Due to the nature of the intervention, it was not possible to blind participants to treatment allocation in this pragmatic trial. In addition, due to the design of the trial, it was not possible for the statistician to be blinded to the treatment allocation. However, collection of self-reported smoking status at 34-38 weeks gestation was initiated blind to treatment allocation.

2.9 Follow-up

Follow-up of participants was undertaken at the engagement stage, 4 week post quit date, 12 week post quit date, 34-38 weeks gestation and six months post-partum (see section 2.9.5.1 for details of changes of the timing of the six months postpartum follow-up). A brief graphical outline of follow-up is given in Figure 1.

2.9.1 Follow-up 1: SSS Engagement

After the participant consented and was informed of group allocation, trial research staff contacted the participant's local SSS to ascertain if the participant attended a first appointment with an SSS advisor and set a quit date. This information was entered into the trial database for both control and intervention group participants. A £50 voucher was automatically dispatched to intervention group participants who attended and set a quit date.

2.9.2 Follow-up 2: Four weeks post quit date

For participants who engaged with the SSS and set a quit date, trial research staff contacted the participant's local SSS four weeks after this quit date to obtain smoking status in the last two weeks and CO breath test result as recorded by the SSS. Where a breath test result was not available from the SSS, trial research nurses collected this directly from the woman in the incentives group to initiate incentive payments. CO breath test results were collected for the control group only where these were available from the SSS in line with national SSS guidelines. This information was entered onto the trial database. If the CO result was at or below the accepted level for a non-smoker at the site, a £50 voucher was automatically dispatched to women in the incentives group.

2.9.3 Follow-up 3: 12 weeks post quit date

For participants in the intervention group who were confirmed quit at four weeks, trial research staff contacted the participant's local SSS eight weeks later to obtain smoking status and CO breath test result as recorded by the SSS. Where this was not available from the SSS, trial research nurses collected this directly from the participant. This information was entered into the trial database. If the CO result was at or below the accepted level for a non-smoker at the site, a £100 voucher was automatically dispatched.

2.9.4 Follow-up 4: Late pregnancy (34-38 weeks gestation)

All participants were followed up at the primary outcome stage in late pregnancy. Follow-up telephone contact was attempted by the trial contact centre at a random date between 34 and 38 weeks gestation allocated at the time of initial randomisation. Trial research nurses reviewed participants' notes one week prior to the telephone contact to check the health status of mother and baby and alert TCC staff to any adverse events e.g. miscarriage or stillbirth, that required particular sensitivity when conducting follow-up. TCC staff were blind to group allocation.

Three attempts were made by the TCC to contact women. If no contact was established, local research staff followed up women by telephone, text, and letter. On successful contact, women were asked: 'Have you smoked in the last 8 weeks?' If yes, 'Have you smoked more than 5 cigarettes in that time?'. EQ-5D-5L data, and current NRT/electronic cigarette use were also collected at this time point.

Self-report of not smoking was corroborated by cotinine estimation on saliva or urine (when saliva collection could not be tolerated). Where women were using NRT or e-cigarettes, anabasine assay on saliva was also conducted. Cotinine and anabasine were assayed by ABS Laboratories Limited (https://www.acmgloballab.com/about-us/our-locations/europe-london-uk). To minimise the potential for women to 'game' the primary outcome, incentive payments were dependent on the CO result, which is an immediate measure, and not on the cotinine or anabasine level.

An important aspect of the primary outcome for this phase III trial is the proportion of women successfully followed up in both the intervention and control group. To minimise loss to follow-up, particularly among controls, women in both groups will receive Love2Shop vouchers of £50 and £25 for providing data and saliva/urine samples where applicable at the primary (late pregnancy) and secondary (six months post-partum) outcome time points respectively (Figure 2.).

To assess if a) women lost to trial follow-up are still smoking towards the end of pregnancy, and b) the primary outcome has been 'gamed' (saliva cotinine below the cut-off but still smoking in late pregnancy) residual blood from routine late pregnancy samples, where available, will be tested.

2.9.5 Follow-up 5: Six months postpartum

Similar to the late pregnancy follow-up all women were contacted at six months after their expected delivery date to ascertain smoking status and collect a saliva/urine sample for those women who self-reported as quit. Quit status six months after birth was ascertained by two sets of questions:
1. 'Have you smoked in the last 8 weeks?' If yes 'Have you smoked more than 5 cigarettes in that time?', and 2. 'Have you smoked since your baby was born?' If yes, 'Have you smoked more than 5 cigarettes in total since your baby was born?'

Follow-up procedures (i.e. no. of contact attempts, data collection and saliva/urine sample collection and assay) were the same as those described for the late pregnancy follow-up. Biological samples of saliva and urine will not be available for use by other researchers.

2.9.5.1 Change to six months postpartum follow-up

Due to funding restrictions, data collection will end on 31/10/2020, and as a result it will not be possible to follow-up all participants to six months postpartum. Approximately 65% of women were followed up at six months postpartum as planned. The remaining 35% were followed up at less than six months postpartum by the TCC, as the follow-up period of the study was not long enough to follow-up these women at six months postpartum. Women who were followed up earlier than six month postpartum were contacted by the TCC between 01/08/2020 and 30/09/2020. Participants who could not be contacted by the TCC during this time period will be followed-up by research nurses up to 31/10/2020.

Table 3: CPIT III Data Collection Schedule

	Timepoint obtained/measured						
	Baseline	**Follow-up 1: SSS Engagement**	**Follow-up 2: 4 weeks post quit date**	**Follow-up 3: 12 weeks post quit date**	**Follow-up 4: Late pregnancy (34-38 weeks gestation)**	**Delivery**	**Follow-up 5: 6 months post-partum**
Age	x						
Height	x						
Weight	x						
Ethnicity	x						
English speaking	x						
Household income	x						
Deprivation quintile	x						
Quality of Life	x				x		x
Event dates	x	x	x	x	x	x	x
Age first smoked	x						
Nicotine dependence level	x						
SSS attendance		x	x	x			
Self-reported smoking status	x		x	x	x		x

	Timepoint obtained/measured						
	Baseline	**Follow-up 1: SSS Engagement**	**Follow-up 2: 4 weeks post quit date**	**Follow-up 3: 12 weeks post quit date**	**Follow-up 4: Late pregnancy (34-38 weeks gestation)**	**Delivery**	**Follow-up 5: 6 months post-partum**
CO breath test result	x	x	x	x	x		x
Quit date		x					
Urine/saliva cotinine/ anabasine					x		x
Current E-cig use	x				x		x
Current NRT use	x	x			x		x
Expected date of delivery	x						
Actual date of delivery						x	
Multiple birth						x	
Birthweight						x	
Stillbirth/ Miscarriage		x	x	x	x	x	
Parity						x	

3 Study Data

3.1 Trial Data

Data extracts without direct identifiers are passed to York Trials Unit from the Database Management Company using sFTP encryption in transit.

3.2 External datasets

Screening logs were received from each site on a monthly basis via the University of York DropOff Service.

Data was downloaded from the following websites to calculate the index of multiple deprivation for postcodes in England, Wales, Scotland and Northern Ireland:

- https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (accessed 08/10/2018, published September 2015)
- https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation/WIMD-2014/wimd2014 (accessed 08/10/2018, published November 2014)
- https://www.gov.scot/Topics/Statistics/SIMD (accessed 08/10/2018, published August 2016)
- https://ons.maps.arcgis.com/home/item.html?id=ef72efd6adf64b11a2228f7b3e95deea (accessed 08/10/2018, published August 2016)

- https://www.nisra.gov.uk/publications/nimdm17-sa-level-results (accessed 27/08/2018, published November 2017)

The postcodes for Northern Ireland were downloaded from the Central Postcode Directory on 27/08/2018, and were published in November 2015. Data from the Central Postcode Directory is not freely available to the public.

3.3 Management of Datasets and Data Verification

The Database Management Company has a long history of managing government related services and is able to demonstrate commitment to data security and quality management through ISO27001 and ISO9001 accreditations and recent GDPR legislation. ISO27001 accredited Information Security Management Systems demand that all of systems and processes are maintained with confidentiality, integrity and availability of data at the core. In addition, the Database Management Company is ISO9001 accredited, the internationally recognized standard for Quality Management Systems. Regular external audits ensure adherence to ISO9001 and ISO27001 standards.

The Business Requirements Specification documents stored in the Y Drive contain comprehensive details of both functional and non-functional requirements of the study database. These documents incorporate all data validation/verification rules applied.

3.4 Location of Data and Associated Files

Data and documents relevant to the statistical analysis will be kept electronically (Y:\ Project -- A - Statistics).

4 Analysis

4.1 Strategy for reporting data and general considerations

Data will be analysed and reported according to CONSORT guidelines [5]. A CONSORT diagram will be produced (see Figure 2). Analyses will be conducted using Stata version 16 or later [6]. The version of Stata to be used will be confirmed in the final report. All analyses will be conducted following the principle of intention-to-treat unless stated otherwise. Statistical tests will be two-sided at the 5% significance level. Effect size estimates will be presented with 95% confidence intervals.

4.2 Recruitment and attrition

The number of participants screened, consented and randomised to the trial will be reported, along with reasons for ineligibility. All withdrawals will be reported along with the reasons, where given, for withdrawal.

4.3 Baseline data

All baseline data will be summarised descriptively by trial arm. In addition, baseline data by trial arm will be presented for those who provided a smoking status at the primary outcome follow-up (Table 4) [7]. No formal statistical comparisons will be undertaken [8]. Continuous measures will be reported as means and standard deviations (and/or median, interquartile range, and minimum and maximum as appropriate) while categorical data will be reported as counts and percentages.

4.4 Primary outcome analysis

The primary outcome will be analysed using a mixed-effects logistic regression model adjusting for treatment group, age, years of smoking, income status (as measured by the IMD quintile within the participant's nation), level of smoking (as measured by the Fagerström score) and whether the primary outcome was collected before the 16th of March

2020 (the date on which the intervention changed due to the Covid-19 pandemic), with centre as a random effect.

For a small number of participants in Belfast, a biochemical sample was provided but due to a miscommunication with the lab the sample was not analysed for anabasine. It was decided with the TSC that in this scenario, those who self-reported as quit and had a CO reading less less than 4 ppm would be classed as non-smokers for the primary analysis.

If a participant is missing data on the primary outcome, it shall be assumed the participant is smoking, as per the Russell Standard [9]. If a participant is missing data on any covariates to be included in the analysis models, the missing values will be replaced with centre-specific means [10]. The assumptions of the model will be checked. If the assumptions are found to be questionable, the data will be transformed or non-parametric data analysis methods will be used.

It was considered whether sparse data bias would be an issue when conducting the primary analysis [11]. Given the sample size calculation assumption that 7% of participants in the control group would quit, it can be assumed that if the full sample size of 940 are recruited and the intervention has no effect, then the 'event' of a participant quitting smoking at the late pregnancy stage would be expected to occur approximately 66 times during the study. The primary analysis model contains five fixed effect variables, which means approximately 13 events per variable are expected. This exceeds the recommended minimum of 10 events per variable when using logistic regression and as a result it was not considered necessary to use an alternative statistical model [12].

4.5 Secondary outcome analyses

Engagement with SSS will be analysed using a mixed-effects logistic regression model adjusting for treatment group, age, years of smoking, income status, level of smoking (as measured by the Fagerström score) and whether the engagement data was collected before the 16th of March 2020, with centre as a random effect.

CO-validated smoking status at 4 weeks post-quit date will be analysed using a mixed-effects logistic regression model, adjusting for treatment group, age, years of smoking, income status, level of smoking (as measured by the Fagerström score) and whether the CO-validated smoking status was collected before the 16th of March 2020, with centre as a random effect. If a participant is missing their smoking status, it shall be assumed the participant is smoking.

Birth weight will be analysed using a mixed-effects linear regression model, adjusting for treatment group, the age, height and weight of the mother at booking, years of smoking, income status, level of smoking (as measured by the Fagerström score) and whether the birthweight data was collected before the 16th of March 2020 as fixed effects, and centre as a random effect. If a participant is missing data on birth weight, it shall be assumed the data is missing at random conditional on the covariates included in the analysis model [13, 14].

Continuous and point abstinence outcomes obtained at six months postpartum will be analysed using mixed-effects logistic regression adjusting for the same covariates and applying the same assumptions used in the primary outcome analysis (with the exception that whether the postpartum point abstinence outcome was collected before 16th of March 2020 will be adjusted for instead of adjusting for whether the primary outcome was collected before the 16th of March 2020). If a participant is missing their smoking status, it shall be assumed the participant is smoking. Participants who at postpartum were followed up earlier than 6 months will be excluded from the analysis of continuous and point abstinence

outcomes obtained at six months postpartum, and will be accounted for in a sensitivity analysis.

4.6 Exploratory outcome analysis

Length of neonatal stay will be summarised descriptively by treatment group.

4.7 Sensitivity analyses

4.7.1 Sensitivity of primary analysis to sparse data bias

To assess the sensitivity of the primary analysis to sparse data bias, the primary outcome will be analysed using a Firth logistic regression model adjusting for treatment group, age, years of smoking, income status (as measured by IMD score), level of smoking (as measured by the Fagerström score), whether the primary outcome was collected before the 16th of March 2020 and site [11]. All variables will be adjusted for as fixed effects, as the Stata command used to implement Firth logistic regression cannot incorporate random effects.

4.7.2 Impact of the Covid-19 pandemic on analysis of the primary and secondary smoking outcomes

To assess the impact of the Covid-19 pandemic on the primary and secondary smoking outcomes, the number of self-reported non-smokers pre-Covid and post-Covid will be compared descriptively by treatment group (Table 6). This will allow assessment of the possibility that participants in the incentives group were more likely to report as non-smokers to receive financial incentives post-Covid compared to pre-Covid. In addition, the number of participants who self-reported as non-smokers but provided a positive biochemical sample pre-Covid and post-Covid will be compared descriptively by treatment group (Table 7).

The number of biochemically verified non-smokers pre-Covid and post-Covid will also be compared descriptively by treatment group (Table 8), in order to assess the possibility that the treatment effect pre-Covid is different to the treatment effect post-Covid.

If the above checks indicate the Covid-19 pandemic had an impact on the analysis of the primary and secondary smoking outcomes, the analyses of these outcomes shall be repeated with the addition of an interaction term between treatment allocation and a pre-Covid/post-Covid variable, with effect size estimates pre-Covid and post-Covid presented alongside corresponding 95% confidence intervals and p-values.

Finally, in order to assess whether the change in intervention had an impact on the return of biochemical samples, the number of returned biochemical samples pre-Covid and post-Covid will be compared descriptively by treatment group in the subset of self-reported non-smokers (Table 9).

4.7.3 Subgroup analyses

The primary analysis will be repeated, with the addition of interaction terms between treatment group and each of the following covariates:

- Maternal age (≤28 years vs >28 years, with 28 years being the mean age of a first time mother according to the ONS in 2015)
- Index of multiple deprivation quintile (1/2/3/4/5)
- Years of smoking (≤10 years vs >10 years)
- Fagerström score (the cut-off will be decided using data on the distribution of the Fagerström score in the previous CPIT RCT)

4.7.4 Missing data analyses

If a participant is missing data on the primary outcome, the participant shall be assumed to be smoking, as per the Russell Standard [9]. The robustness of the primary analysis to this assumption will be explored using two methods.

The first method will use multiple imputation by chained equations [15]. Missing values of baseline covariates will be replaced with centre-specific means. The imputation model for the biochemically verified smoking status at late pregnancy will include the baseline covariates used in the primary analysis, the treatment allocation, engagement with SSS, CO-validated smoking status at 4 weeks post-quit and biochemically verified point abstinence at 6 months post-partum.

Each imputed dataset will be analysed using the primary analysis model. The estimates obtained from analysis of the imputed datasets will then be combined using Rubin's rules.

The second method will explore the sensitivity of the results to the missing data mechanism using a pattern mixture model, which will be implemented using the `rctmiss` command in Stata [16]. The pattern mixture model expresses assumptions about the missing data mechanism in the form of a logistic regression model regressing the outcome on a set of covariates and a missing data indicator, whose parameter shall be denoted as β_m. The Russell standard is equivalent to assuming that $\beta_m = -\infty$ i.e. missing=non-quitter. Negative values of β_m assume that participants with missing smoking status are less likely to have quit than participants with non-missing smoking status, while positive values assume that participants with missing smoking status are more likely to have quit than participants with non-missing smoking status. The consequences of varying β_m over a range of values shall be explored and displayed graphically.

4.7.5 Impact of participants who were followed up at postpartum earlier than the planned 6 months

The number and proportion of participants who were followed up earlier than 6 months postpartum will be summarised descriptively by trial arm. The time in months between the planned follow-up date and actual follow-up date will be summarised descriptively by trial arm.

Participants who provide a smoking status postpartum will be grouped by whether the postpartum follow-up took place between:

- Less than two months postpartum
- More than or equal to two months postpartum and less than four months postpartum
- More than or equal to four months postpartum and less than six months postpartum
- More than or equal to six months postpartum

Within these groups, the number and proportion of participants who were cotinine/anabasine validated non-smokers will be summarised descriptively.

4.7.6 Sensitivity of primary analysis to assumption regarding participants with missing anabasine test

In the primary analysis it will be assumed that for those participants who provided a biochemical sample but due to a miscommunication with the lab were not tested for anabasine, that if they have a CO reading less than 4 ppm then they are non-smokers. The impact of this assumption on the primary analysis will be explored by repeating the primary analysis under two different scenarios. The first scenario will assume that the participants in the incentives group were smokers while the participants in the control group were non-

smokers. The second scenario will assume the participants in the incentives group were non-smokers while the participants in the control group were smokers.

4.8 Compliance with intervention

A CACE analysis for the outcome of birth weight will be used to obtain an unbiased estimate of the effect of the intervention with full compliance (defined as the participant being found to be a biochemically verified non-smoker at late pregnancy). An instrumental variable model will be used, using the compliance variable as the endogenous variable, and treatment group, the age, height and weight of the mother at booking, years of smoking, income status, level of smoking (as measured by the Fagerström score), whether the engagement data was collected before the 16th of March 2020, and centre as exogenous variables.

4.9 Gaming of the intervention

To assess the extent to which participants 'gamed' the primary outcome i.e. stopped smoking a few days before sample collection, the number and proportion of women who were found to be biochemically verified non-smokers but tested positive for smoking in late pregnancy residual blood samples (where available) will be summarised descriptively by treatment group.

4.10 Cotinine and anabasine test results

For participants who reported as non-smokers and using e/cigarettes or NRT at late pregnancy, the results of the cotinine and anabasine tests will be summarised descriptively, in order to assess the impact of anabasine testing on the derivation of the primary outcome (Table 10). The analysis will be repeated for the 6 months post-partum time point.

4.11 Adverse events

Adverse events related to the study will be presented descriptively by treatment group.

4.12 Planned interim review and analyses

No formal interim analyses will be undertaken.

5 SAP amendment log

Amendment/addition to SAP and reason for change	New version number, name and date
The derivation of biochemically verified smoking status was changed in line with the latest cut-offs advised by ABS laboratories (Table 2). A descriptive analysis of cotinine and anabasine results was added (Section 4.10 and Table 10). Amendment of analysis of smoking status at 4 weeks, birth weight and sparse data sensitivity analysis to include additional covariates (Sections 4.5, 4.7.1 and 4.8). For all three analyses, whether the outcome was collected before the 16th March 2020 was included as an additional covariate. For the analysis of birth weight, years of smoking, income status and level of smoking were also included as additional covariates.	CPIT III Statistical Analysis Plan_1.1_20210728

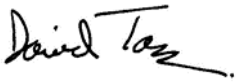
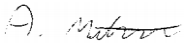
6 Signatures of approval

6.1 Contributions

AM and AK drafted the Statistical Analysis Plan; however, sections of this document have been copied and/or adapted from the trial protocol. This document will be reviewed by members of the TMG and TSC.

6.2 Signatures

Sign-off of the Statistical Analysis Plan by, as a minimum, the person writing the SAP, a relevant senior statistician, and the Chief Investigator.

Name	Trial Role	Signature	Date
Prof. David Tappin	Chief Investigator		29/07/2021
Prof. Linda Bauld	Chief Investigator		05/08/2021
Alex Mitchell	Study Statistician		28/07/2021
Prof. Catherine Hewitt	Senior Statistician		28/07/2021

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8 Appendices

8.1 Scoring of Fagerström Test for Nicotine Dependence

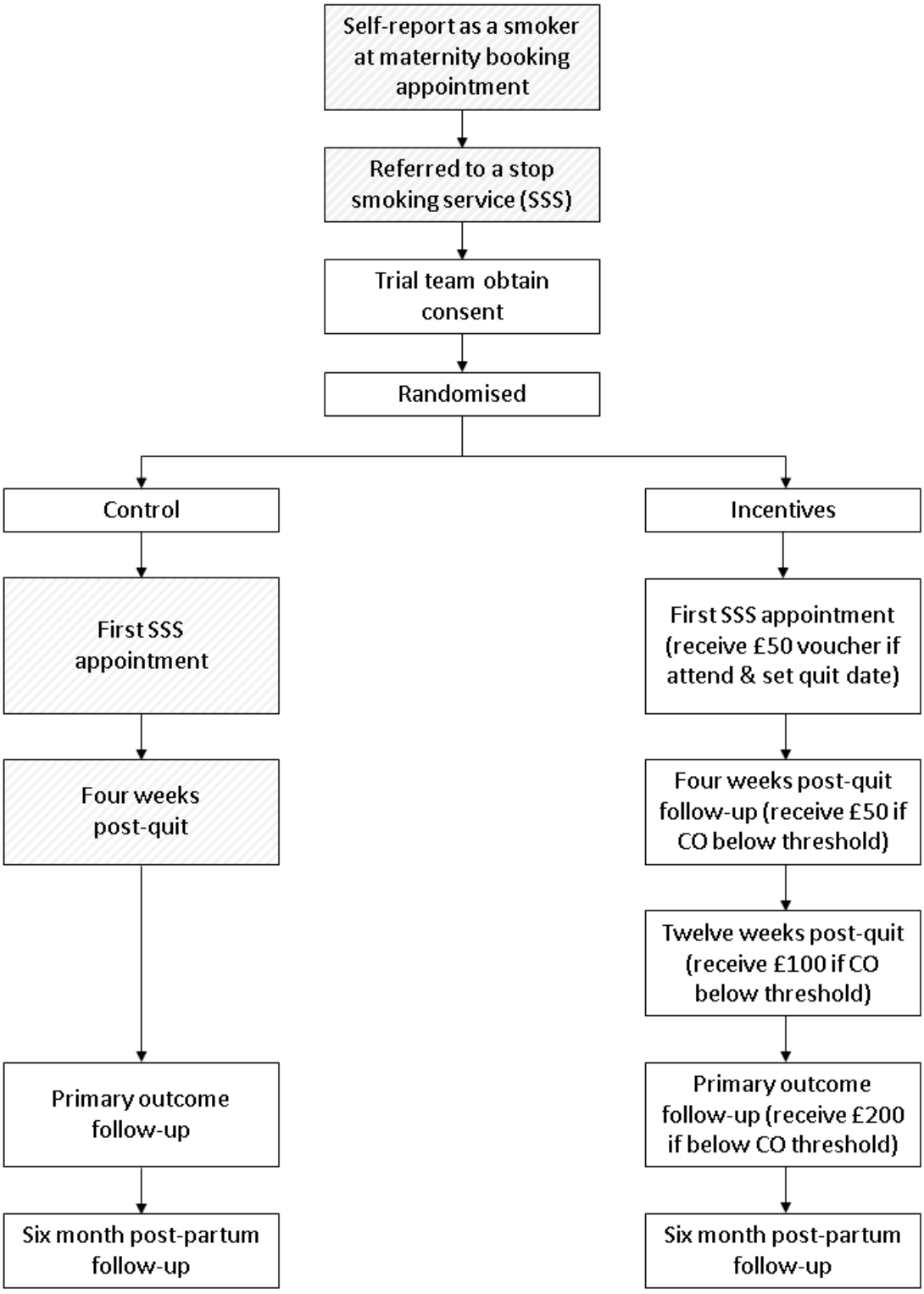
The Fagerström Test for Nicotine Dependence is scored in the following manner:

- How soon after waking do you smoke your first cigarette?
  - (3) Within 5 minutes
  - (2) 5-30 minutes
  - (1) 31-60 minutes
- Do you find it difficult to refrain from smoking in places where it is forbidden?
  - (1) Yes
  - (0) No
- Which cigarette would you hate to give up?
  - (1) The first in the morning
  - (0) Any other
- How many cigarettes a day do you smoke?
  - (3) 31 or more
  - (2) 21-30
  - (1) 11-20
  - (0) 10 or less
- Do you smoke more frequently in the morning?
  - (1) Yes
  - (0) No
- Do you smoke even if you are sick in bed most of the day?
  - (1) Yes
  - (0) No

The Fagerström score is calculated by adding up the scores from each question, and can take values between 0 and 10. There is no published advice in regards to how to account for missing responses to the Fagerström questionnaire.

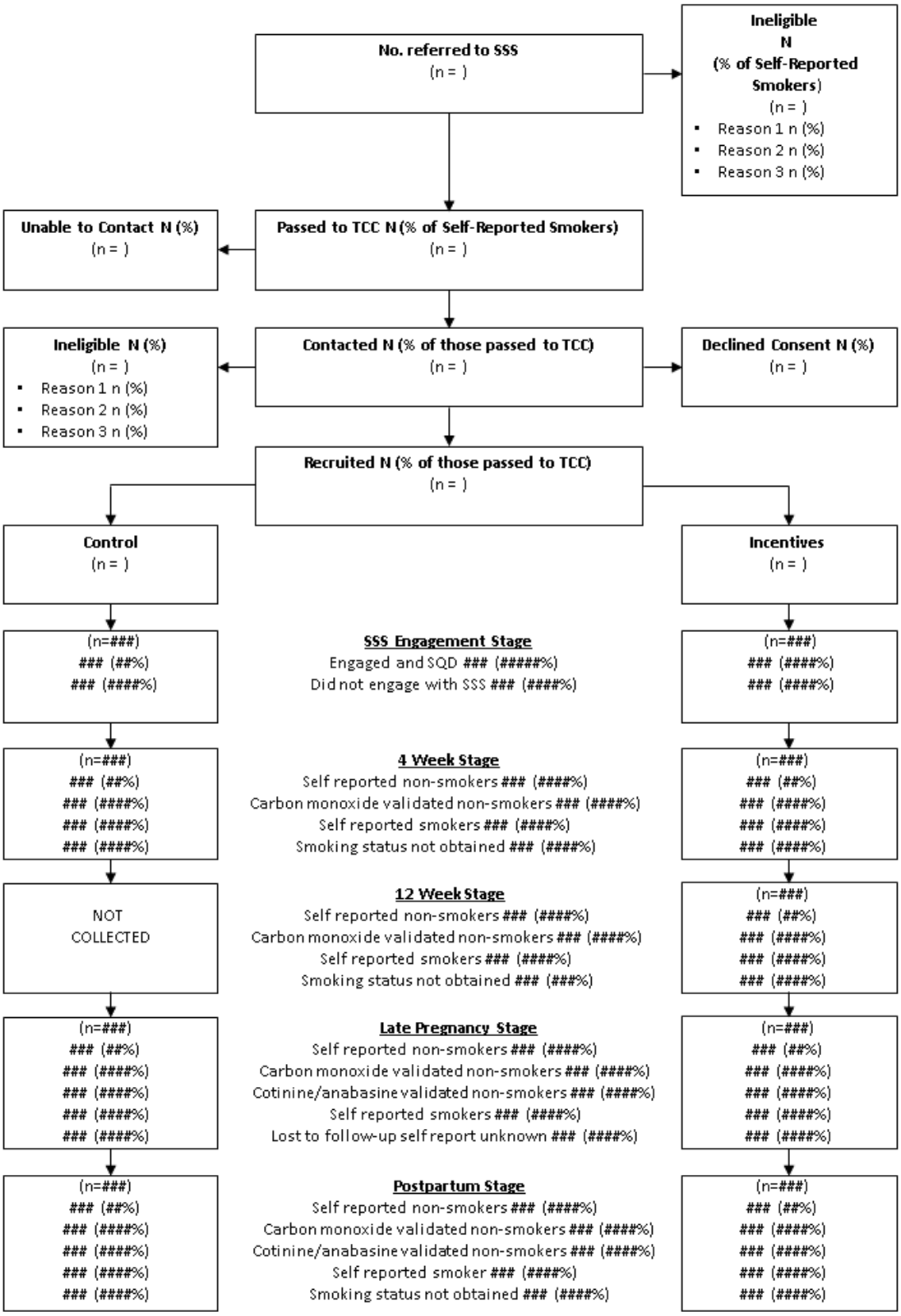
8.2 Trial flow diagram

Figure 1: A trial flow diagram detailing the flow of participants through the study and the incentives on offer to the intervention group. The shaded boxes indicate the trial team is not involved in this follow-up stage.



8.3 CONSORT diagram

Figure 2: A CONSORT diagram for CPIT III.



8.4 Example tables

8.4.1 Baseline characteristics

Table 4: Baseline characteristics for all participants and for participants who provided a cotinine/anabasine verified smoking status at the primary outcome follow-up.

	All randomised participants		**Participants who provided a smoking status at the primary outcome stage**	
	Control (n=)	**Intervention (n=)**	**Control (n=)**	**Intervention (n=)**
Height, m n (%) Mean (SD)				
Weight, kg n (%) Mean (SD)				
BMI, kg/m^2 n (%) Mean (SD)				
Ethnicity, n (%)				
Maternal age at booking, years n (%) Mean (SD)				
Previous live births Median (range)				
Index of multiple deprivation, n (%) 1st quintile (most deprived) 2nd quintile 3rd quintile 4th quintile 5th quintile (least deprived)				
CO reading at maternity booking, ppm n (%) Mean (SD)				
First cigarette within 5 minutes of waking, n (%) Within 5 minutes 5-30 minutes 31-60 minutes				
Difficulty not smoking in forbidden places, n (%) Yes No Missing				
1st cigarette most difficult to give up, n (%) The first in the morning Any other Missing				
Cigarettes smoked a day, n (%) 10 or less 11-20 21-30 31 or more Missing				
Smoke more frequently in the morning, n (%)				

Yes No Missing				
Smoke even if sick in bed most of the day, n (%) Yes No Missing				
Fagerström score n (%) Mean (SD)				
Partner smokes, n (%) Yes No Missing				
Age at which participant started smoking, years n (%) Mean (SD)				
Uses NRT n (%) Yes No Missing				
Uses e-cigarettes n (%) Yes No Missing				

Table 5: Primary and secondary analyses

	Number of events/Number in group	**Adjusted odds ratio (95% CI)**	**p-value**
Late pregnancy Incentives Usual care			
Engagement with SSS Incentives Usual care			
4 week post-quit Incentives Usual care			
6 months post-partum (continuous abstinence) Incentives Usual care			
6 months post-partum (point abstinence) Incentives Usual care			

Table 6: Comparison by treatment group of self-reported smoking status pre-Covid and post-Covid

	Incentives		**Usual care**	
	Pre-Covid	**Post-Covid**	**Pre-Covid**	**Post-Covid**
4 week, n (%)				

	Incentives		Usual care	
	Pre-Covid	**Post-Covid**	**Pre-Covid**	**Post-Covid**
Non-smoker Smoker				
12 week, n (%) Non-smoker Smoker				
Late pregnancy, n (%) Non-smoker Smoker				
6 months post-partum, n (%) Non-smoker Smoker				

Table 7: Comparison by treatment group of the number of participants who provided a positive biochemical sample, in the subset of participants who self-reported as non-smokers and provided a biochemical sample

	Incentives		Usual care	
	Pre-Covid	**Post-Covid**	**Pre-Covid**	**Post-Covid**
Self-reported as non-smoker and tested positive in biochemical sample, n (%) Late pregnancy 6 months post-partum				

Table 8: Comparison by treatment group of biochemically verified smoking status pre-Covid and post-Covid

	Incentives		Usual care	
	Pre-Covid	**Post-Covid**	**Pre-Covid**	**Post-Covid**
4 week, n (%) Non-smoker Smoker				
12 week, n (%) Non-smoker Smoker				
Late pregnancy, n (%) Non-smoker Smoker				
6 months post-partum, n (%) Non-smoker Smoker				

Table 9: Comparison by treatment group of the number of participants who provided a biochemical sample, in the subset of participants who self-reported as non-smokers

	Incentives		Usual care	
	Pre-Covid	**Post-Covid**	**Pre-Covid**	**Post-Covid**
Provided a biochemical sample, n (%) Late pregnancy 6 months post-partum				

Table 10: Anabasine results presented by treatment group and cotinine result for patients who reported as non-smokers and reported using e-cigarettes or NRT.

	Cotinine			
	Incentives		**Usual care**	
	<10ng/ml	**≥10ng/ml**	**<10ng/ml**	**≥10ng/ml**
Anabasine result, n (%) ≤0.2 >0.2				