Open-label randomised controlled trial of enhanced support and nicotine replacement therapy (NRT) offered for preloading, lapse recovery and smoking reduction: impact on smoking in pregnancy

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Short title: ***S***moking, ***N***icotine ***A***nd ***P***regnancy **3** Trial

Acronym: **SNAP-3 Trial**

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SYNOPSIS

Title	Open-label randomised controlled trial of enhanced support and nicotine replacement therapy (NRT) offered for preloading, lapse recovery and smoking reduction: impact on smoking in pregnancy
Acronym	SNAP 3 Trial
Short title	***S***moking, ***N***icotine ***A***nd ***P***regnancy 3 Trial
Chief Investigator	Tim Coleman (CI) and Miranda Clark (DCI)
Objectives	Primary Objective 1 To compare effectiveness of usual care (UC) plus enhanced support for preloading and lapse recovery and NRT offered for preloading with UC alone for promoting prolonged smoking cessation in pregnancy Secondary Objectives 1 To investigate incremental cost-effectiveness of usual care (UC) plus enhanced support for preloading and lapse recovery and NRT offered for preloading with UC alone for prolonged smoking cessation in pregnancy 2 To compare the effects of UC plus enhanced support for preloading, lapse recovery and smoking reduction and NRT offered for preloading and smoking reduction with UC alone on: a. Validated 7-day abstinence from smoking in late pregnancy b. Reported 50% reduction in smoking c. Exhaled CO at delivery d. Maternal, foetal and neonatal birth outcomes 3 To identify barriers against and facilitators for participation within women offered enrolment such that recruitment can be optimised.
Trial Configuration	Randomised, controlled, parallel group, open-label multicentre assessor-blind trial
Setting	Participants will be recruited through hospital or community antenatal care or the internet; trial interventions will be initiated in antenatal settings but will mainly be delivered remotely by telephone or video call and will be experienced in locations of participants' choice.
Sample size estimate	Assuming a 10% quit rate in the control group and a 5% significance level, a study of 1430 participants (715 per arm) will have 90% power to detect an absolute increase of 6% (odds ratio 1.7) in validated cessation rates between the treatment groups.

Number of participants	1430
Eligibility criteria	**Population/inclusion criteria** Women of any age who are < 25 weeks' gestation and have been referred for or have received or attended an appointment as part of standard antenatal care; smoke ≥ 5 daily cigarettes; agree to set a quit date; accept referral to SSS, use e-cigarettes less than daily and are willing to use NRT, able to understand English and give informed consent. **Exclusion criteria** Already in a cessation study; using e-cigarettes daily or more frequently; contraindications to NRT including: severe cardiovascular disease, unstable angina, cardiac arrhythmias, recent cerebrovascular accident or TIA, chronic, generalized skin disorders or sensitivity to nicotine patches,; major foetal anomalies.
Description of interventions	**Control group** Usual care - This comprises 'Very Brief Smoking Advice on Smoking for pregnant women' (VBA), carbon monoxide (CO) testing, advice on quitting with support, including NRT and, referral for intensive support which includes an offer of NRT to assist quit attempts. **Intervention** Delivered in addition to usual care, this has three components. All three involve enhanced behavioural support to promote NRT use; two also involve offers of NRT: i) NRT patch offered as '**preloading**', used up to 4 weeks before Quit Date, after which usual care support begins ii) After usual care support begins and women receive NRT to help them quit as part of this, participants are advised to **continue NRT** should they experience any brief smoking lapses. For intervention arm women who are *still smoking* 6 weeks from randomisation: iii) NRT offered as patch or inhalator and ***used to reduce smoking*** and induce cessation
Duration of study	Planned start date is 1st October 2020 with a 4-year duration. Participants will be in the study from enrolment (~ 12 weeks gestation, on average) until childbirth.
Randomisation and blinding	Women will be randomised to the intervention or control group in a 1:1 ratio. The randomisation schedule will be stratified by site and level of nicotine addiction and based on a computer generated pseudo-random code using random permuted blocks of varying size. Participants will not be blinded to treatment allocation but primary outcome data will be collected by researchers blind to allocation.

Outcome measures	***Primary outcome*** Biochemically validated, prolonged abstinence from smoking reported between six weeks after randomisation and 36 weeks gestation or childbirth, whichever is earlier. ***Secondary outcomes*** Smoking-related • reported 7-day smoking abstinence at 6 weeks after randomisation • reported and validated 7-day smoking abstinence at 36 weeks gestation • reported ≥ 50% reduction in daily cigarettes at 36 weeks gestation • exhaled CO concentration at delivery • whether or not brief smoking lapse experienced, reported at 6 weeks post randomisation Pregnancy and safety-related • miscarriage • stillbirth • low birth weight for gestational age • unadjusted birthweight and birthweight z score • premature birth • gestation at birth • congenital abnormality • mode of delivery • admission to special care • neonatal death ***Exploratory outcomes*** • cigarettes per day when using NRT for 'preloading' or to cut down smoking exhaled CO when using NRT for 'preloading' or to cut down smoking • saliva cotinine concentration when using NRT for 'preloading' or to cut down smoking • use of stop smoking support •
Statistical methods	Trial analysis and reporting will be in accordance with CONSORT guidelines. The primary analysis will use the intention-to-treat population and it will be assumed those lost to follow up as smoking. The primary outcome will be analysed using a mixed-effect logistic regression model adjusting for randomisation stratification variables with a random effect for site. Absolute and relative measures of effect between groups with 95% confidence intervals will be presented. Secondary outcomes will be analysed using regression models appropriate to the type of outcome variable.

ABBREVIATIONS

AE	Adverse Event
API	Application Programming Interface
CI	Chief Investigator
CO	Carbon Monoxide
cpd	cigarettes per day
CRF	Case Report Form
CRN	Clinical Research Network
DCI	Deputy Chief Investigator
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
MHRA	Medicines and Healthcare products Regulatory Agency
NCSCT	National Centre for Smoking Cessation Training
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
NRT	Nicotine Replacement Therapy
PI	Principal Investigator at a local centre
PPI	Patient and Public Involvement
PIS	Participant Information Sheet
QD	Quit Date
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event

SIP Smoking in Pregnancy

SmPC Summary of Product Characteristics

SSS Stop Smoking Service

TMG Trial Management Group

TSC Trial Steering Committee

VBA Very Brief Advice (for smoking cessation)

DEFINITIONS:

Site trial staff: Clinical Research Network (CRN) staff, research nurses, research midwives or any local site staff delegated by the site PI

Central research team: SIP researchers, SIP administrators or any staff delegated by the CI

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Smoking in pregnancy (SIP) is the biggest reversible cause of miscarriage, stillbirth, prematurity, low birth weight (LBW), perinatal, neo-natal and sudden infant death and poorer infant cognition and behavioural outcomes.[1-3] Smoking cessation interventions have been shown to reduce premature birth and LBW, which cause considerable infant morbidity.[4] Additionally, for women who do not stop smoking completely, reducing SIP is beneficial; lighter smoking, validated using exhaled carbon monoxide, is strongly associated with better birth outcomes.[5-7] SIP is a major international public health problem; prevalence is 13% to 25% in high income countries [8-11] and a similar epidemic is developing in low and middle income ones.[12] In England in 2017/8, 11% of women were smoking at childbirth with rates highest in economically-deprived areas (Blackpool 26%) and in England and Wales around 94,600 foetuses are exposed to SIP annually.[13]

Stopping smoking prevents harms from SIP but few pharmacological cessation interventions can be used in pregnancy. Nicotine replacement therapy (NRT) is widely offered because it is very plausibly less harmful than smoking; varenicline, the most effective drug, is contra-indicated. NRT provided with or without behavioural support increases cessation in the general population RR 1.55 (1.49 to 1.61), with no clear evidence that one form (e.g. patch or gum) works better than another.[14] However, NRT – mainly tested as standard dose patches or gum - appears less effective in pregnancy [RR (95% CI) 1.41 (1.03 to 1.93)],[15] most likely because nicotine metabolism is faster in pregnancy and so higher NRT doses are needed to prevent nicotine cravings and to exert effects.[16 17]

Some ways of using NRT have been shown to be more effective for non-pregnant people. For example *preloading*, using NRT for 2-4 weeks before attempting to quit smoking improves smoking abstinence at six [RR 1.25 (1.08 to 1.44)][18] and 12-months [OR 1.28, 95% CI (0.97 to 1.69)].[19 20] Additionally, in those who successfully use NRT to cut down rather than to stop smoking completely, long-term abstinence unexpectedly increases [RR 1.87 (1.43 to 2.44)].[21] Furthermore, when NRT is continued and not stopped during brief smoking lapses or slip ups, occurring during quit attempts, this is strongly associated with continued abstinence.[22] Secondary analyses from a large, double-blind, placebo-RCT found that 'quitters' who continued NRT when brief smoking lapses occurred were much more likely to be abstinent at 6 and 10 weeks than those similarly using placebo [(8.3% versus 0.8%; RR, 11.0, 95% CI,(2.59 to 48.72) and (9.6% versus 2.6%; RR, 3.7, 95% CI (1.61 to 8.43)] respectively.[22] Similarly, in a RCT, amongst quitters who had lapses, 7-day quit rates at 4 months amongst those advised to continue and stop NRT were 51% and 46% respectively (not statistically significant).[23]

Clearly, there is scope to improve smoking cessation rates for pregnant women by supporting them to try using NRT in these ways and there is now sufficient evidence that NRT is safer than smoking in pregnancy to justify doing so.

NRT safety in pregnancy

Elimination of toxins released by tobacco combustion: NRT exposes users to nicotine without the numerous toxins and carcinogens released when tobacco is burned. Hence, NRT could only be more harmful than SIP if nicotine causes a substantial burden of tobacco-related harm; however, this is very unlikely. A Cochrane review of 9 RCTs (2336 women) gives no indication that NRT compared to SIP and used for cessation worsens pregnancy outcomes but is indicative of NRT being protective.[15] This found that, women who smoked in pregnancy and then used NRT had heavier (i.e. healthier) babies [mean difference, (95% CI) compared to those who used none 99.73g, (-6.65g to 206.1g)]. Additionally, a large placebo-

controlled RCT, found better infant development at 2 years amongst NRT-exposed foetuses, with a dose-response relationship between adherence to NRT and development [odds ratio, (95% CI) for unimpaired infant development following NRT compared with placebo, 1·40, (1·05 to 1·86)].[24] Available, large observational studies do not add to this evidence because they inadequately measure or adjust for women's smoking behaviour before, after or during NRT use.[25] Overall, evidence suggests that in pregnancy, nicotine is not a substantial cause of tobacco-related harms and NRT is safer than smoking.

Pregnant women's nicotine and tobacco smoke exposure is less when they use NRT: As nicotine most probably causes only a small proportion of tobacco-related harms, NRT could only prove more harmful to pregnancies than smoking, if compared to SIP, it greatly increases pregnant women's exposure to nicotine. However, this is improbable as pregnant women who have become abstinent from smoking and who use NRT, receive much less cotinine (major metabolite of nicotine); a systematic review found 70.3ng/ml lower mean cotinine concentrations from NRT compared to smoking (range of mean cotinine levels when smoking, +99 to +246ng/ml).[26] Additionally, NRT users who smoke concurrently, smoke fewer cigarettes. When non-pregnant people preload with NRT patches, the mean number of daily cigarettes falls [13.4 vs 15.7, (mean diff, -2.6, 95% CI, -3.2 to -2.1)] and they exhale less carbon monoxide (CO) - a proxy for tobacco smoke exposure – (mean CO, 20.4 vs 23.6ppm, mean diff, -3.2ppm, 95% CI, -4.0 to -2.3)].[27] Similarly, when people use fast-acting NRT (e.g. gum or inhalator) to cut down smoking, exhaled carbon monoxide (CO) concentrations fall by 13% to 40%; nicotine and cotinine concentrations are mostly lower too (range of percentage changes, -29 to +6%).[28] Non-pregnant people who use slower-acting NRT patches to cut down smoking have 36% lower CO concentrations and smoke 55% fewer daily cigarettes, but have only a 5% higher mean saliva cotinine concentration (all absolute % changes).[29]

Pregnant women who use NRT patches to cut down smoking behave similarly. For example, compared to when smoking, women on NRT patches who smoked concurrently, smoked fewer weekly cigarettes [mean diff (MD) -48, 95% CIs -52 to -38] and exhaled less CO (MD -3ppm, 95% CI -4 to -2ppm), but had similar cotinine concentrations (118ng/ml vs 111 ng/ml, mean difference (ratio of) geometric means, 0.94, 95% CIs 0.83 to 1.07).[30]

Current support for stopping smoking in pregnancy

In the UK, NICE recommends NRT for women who cannot stop smoking[31] and all UK SSS offer NRT in pregnancy.[32] Currently, pregnant women who use NRT set a quit date (QD) on which a quit attempt begins and, they start NRT. Women are encouraged to stop smoking abruptly and not smoke at all in quit attempts, the 'Not a Puff' rule.[33] Although pregnant 'quitters' lapse to smoking a median of 4 times the second and third trimesters[34], there is no UK guidance on use of NRT during brief smoking lapses. However, many pregnant women have concerns about nicotine safety such that, if they lapse by smoking even a little, they stop NRT and keep on smoking rather than continuing with NRT and trying to stop.[35] Qualitative work suggests smoking cessation practitioners infrequently advise on lapse management and when they do, this is usually responsive to women's mention of lapses and lapse management is not routinely mentioned.[36] NICE recommends non-pregnant people to use NRT to reduce smoking[37] but does not specifically advise pregnant women who smoke to do so and currently, if pregnant smokers do not want to try stopping smoking completely, the NHS does not offer further support.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To determine the combined effect of enhanced support for preloading, lapse (slip ups) recovery or smoking reduction and of NRT offered for preloading or smoking reduction added to usual smoking cessation care on i) smoking cessation and ii) pregnancy/infant outcomes.

PRIMARY OBJECTIVE

To compare effectiveness of usual care plus enhanced support for preloading and lapse recovery and NRT offered for preloading with usual care alone for promoting prolonged smoking cessation in pregnancy

SECONDARY OBJECTIVES

1. To investigate incremental cost-effectiveness of usual care plus enhanced support for preloading and lapse recovery and NRT offered for preloading with usual care alone for prolonged smoking cessation in pregnancy.
2. To compare the effects of usual care plus enhanced support for preloading, lapse recovery and smoking reduction and NRT offered for preloading and smoking reduction with usual care alone on:
    a. Validated 7-day abstinence from smoking in late pregnancy
    b. Reported 50% reduction in smoking
    c. Exhaled CO at delivery
    d. Maternal, foeatal and neonatal birth outcomes
3. To identify barriers against and facilitators for participation within women offered enrolment such that recruitment can be optimised

DETAILS OF PRODUCT(S)

The trial intervention is an advice and behavioural support package on how to use NRT to best promote smoking cessation in pregnancy, which involves direct provision of some NRT. The MHRA have adjudicated that it is not a Clinical Trial of an Investigational Medical Product and products listed below are not IMPs.

Description

As part of usual care, participants from both trial groups will be offered whatever NRT products are routinely provided by NHS Stop Smoking Services for use in quit attempts (see '*Study Interventions*')

For women in the Intervention Group only, alongside enhanced behavioural support, two NRT products will be offered:

i) 15mg/16hr nicotine patches – during preloading stage, lapse recovery and smoking reduction phase;
ii) 15mg NRT inhalator cartridges (maximum 6 cartridges per day) – during smoking reduction phase, as an alternative to the patch.

Manufacture

Packaging and labelling

All trial NRT products will be supplied in the sealed packs as provided by the manufacturers and used in a manner which is consistent with manufacturers' instructions as detailed within packs. A trial-specific label will clearly identify that products are for use in the study only.

Storage, supply and return

Nottingham University Hospitals Clinical Trials Pharmacy will order the NRT products upon receipt of a written order from the Smoking in Pregnancy research office and will order in batches over the trial period to ensure the stock remains in date. The trial supplies will be stored securely in the pharmacy below 25^{o}C, separate to other supplies. Before being released to the research team, the products will be over-labelled with a trial specific label and will undergo QC release to the Smoking in Pregnancy Research office, Tower Building, University Park, Nottingham NG7 2RD.

Receipt: Upon receipt of the product at the research office, the Trial Manager/ Trial Administrator will sign for the delivery and check contents and record the products received on the accountability log. If there are any discrepancies, the study team will alert the Trials pharmacy. The temperature in the storage area will be logged on arrival.

Supplies will be stored securely in a locked cabinet within the research office and will only be accessible to the Trial Manager and the Trial Administrator. Here stock will also be stored below 25^{o}C in line with the manufacturer's guidance. A week-day temperature log will be kept. The Trial Manager will note in the trial deviation log any temperature breach of more than 24 hours or times when the thermometer is not working. The Clinical Trials Pharmacist will be informed of all deviations as these are documented and will advise on any actions required (e.g. quarantine or destruction of affected products).

Upon randomisation of a participant, the research office will be automatically alerted via email to a trial specific address from a Nottingham Clinical Trials Unit (NCTU) web-based system. Intervention group participants will receive a starter pack, including NRT patches, prior to their first preloading phone call with the central research team smoking cessation advisor.

Further NRT Supplies (see '*Study Interventions*'): Participants in both groups may receive NRT as and when required from their local stop smoking services during their quit attempt. During an agreed pre-loading phase, participants will be contacted weekly by the central research team and offered further NRT if required. During a reduction/cessation phase, participants who are eligible for this intervention component will be contacted by the central research team every 2 weeks and offered further NRT supplies, if appropriate.

All despatched NRT will be labelled with the participant ID and initials and sent via Royal Mail recorded delivery. In the NHS this is a standard 'direct supply' method used by some SSS. The NRT will not be temperature-regulated during transportation as this is not standard in the NHS. The posting date and the participant ID number will be recorded on an electronic log along with the quantity and strength of medication supplied.

Receipt by participant: central research staff will track receipt of trial medication and will contact women shortly after NRT has been received or should have been. If necessary, NRT will be re-sent via recorded delivery using Royal Mail.

Participants will be advised to dispose of unused NRT and packaging, as per the manufacturer's instructions. Any unused trial supplies which are not issued to participants will be returned to the trial pharmacy; this will be recorded in the pharmacy trial master file and the accountability log.

Any recall alerts will be flagged through the NUH procurement process and the Clinical Trials pharmacy will notify the Trial Manager who will review the accountability logs for stock held

and supplied. Any affected stock will be quarantined and the sponsor informed. Participants who have been sent supplies of affected NRT product(s) will be contacted and asked to stop using this / these.

Placebo

There is no placebo.

Known Side Effects

The side effects of NRT are well known and are clearly described in patient information leaflets which accompany licensed products. Nicotine is an irritant and, irrespective of delivery method, NRT users may experience minor side effects due to local irritation. However, NRT is generally well tolerated; serious side effects are rare and, generally NRT is considered much less risky for users than continued smoking.

Known side effects for 15mg/16hr nicotine patch occurring in at least 1 in 100 users and listed in the product SmPC include: rash/local skin irritation; nausea/vomiting; headaches & dizziness. Similarly, for NRT inhalator these common reactions include, headache; local sensitivity; burning sensation and paraesthesia; dizziness; dysgeusia; cough and throat irritation; fatigue and minor gastrointestinal symptoms.

Reference sources are SmPCs for Nicorette Invisipatch (section 4.8, version: 30th December 2019) and Nicorette 15mg Inhalator (section 4.8, version: 30th December 2019). Any rare side effects mentioned there but not here, will also be considered as expected.

In addition to the above products being offered to intervention group participants, participants from both groups may be offered NRT as part of usual care delivered by stop smoking services commissioned by local authorities or the NHS. It will be monitored which products are used as usual care by participants.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

An individually randomised, two arm, parallel, open-label RCT recruiting from antenatal settings; a pragmatic design for evaluating impacts on an intervention combining enhanced behavioural support and offer(s) of NRT in an NHS context. There will be an 'in trial' pilot phase to demonstrate to funders that the full trial is deliverable at 9 months recruitment.

Primary endpoint

Biochemically validated, prolonged abstinence from smoking reported between six weeks after randomisation and 36 weeks gestation or childbirth, whichever is earlier.

Smoking lapses are permitted during this period, provided no more than 5 cigarettes in total are smoked[38] and a 7-day period of total abstinence is reported immediately before primary outcome follow up.

Secondary endpoints

Smoking-related

- reported 7-day smoking abstinence at 6 weeks after randomisation
- reported and validated 7-day smoking abstinence at 36 weeks gestation
- reported ≥ 50% reduction in daily cigarettes at 36 weeks gestation
- exhaled CO concentration at delivery

- whether or not brief smoking lapse experienced, reported at 6 weeks post randomisation

NB: If delivery occurs before 36 weeks gestation, outcomes intended for collection at 36 weeks will be collected then.

Pregnancy and safety-related

- miscarriage
- stillbirth
- low birth weight for gestational age
- unadjusted birthweight and birthweight z score
- premature birth
- gestation at birth
- congenital abnormality
- mode of delivery
- admission to special care
- neonatal death

Exploratory outcomes

- exhaled CO and cigarettes smoked per day when using NRT for 'preloading' or to cut down smoking
- saliva cotinine concentration when using NRT for 'preloading' or to cut down smoking
- use of stop smoking support
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Stopping rules and discontinuation
There are no formal interim analyses planned and no stopping rules as the study is very low risk to participants and the hazards of using NRT are well defined and compare favourably to smoking (see Adverse Events); the DMC will periodically review and monitor accumulating data, usually every 6-12 months, making recommendations as appropriate.

Recruitment: At least 26 acute trusts with high SIP and deprivation rates will be selected as trial centres, aiming for these to have SSS support available locally. To achieve target sample size within 30 months, it is expected that 26 sites will be required to recruit one or two participants per month on average during the complete recruitment period (mean monthly recruitment ~ 1.8 participants). There will be an 'in trial' pilot phase which aims to demonstrate to funders that the full trial is deliverable. The pilot will last 9 months from the start of recruitment. The aim is to recruit 385 participants during the pilot.

Completeness of primary outcome ascertainment: In cessation studies, participants who re-start smoking usually stop cessation treatments; many are lost to follow up but it is standard to assume they are smoking. Hence, study retention is less important than completeness of outcome ascertainment.

Addressing contamination: Consideration will be given to halt the trial in the unlikely event of finding a contamination rate attributable to health professionals' actions exceeding 15%. Contamination is defined as using NRT in a manner which is contrary to treatment allocation; this will not always be due to health professionals' advice. During the pilot, cases of contamination will be investigated by interviewing recruiting sites or SSS staff involved, or a random sample if cases are too numerous. It will be attempted to understand contamination

issues, and so derive ways of minimising future occurrences and will close centres if there is a centre-specific problem that cannot be rectified.

Progression after 'in-trial' pilot phase: There will be an 'in trial' pilot phase which aims to demonstrate to funders that the full trial is deliverable. The pilot will last 9 months from the start of recruitment. Progression of the trial beyond the pilot phase will be contingent on meeting progression criteria which have been approved by the study funder. At the end of the in-trial pilot, the Trial Steering Committee and the funder will assess to what extent progression criteria have been met, and will recommend on actions required.

RANDOMISATION AND BLINDING

Participants will be allocated to the intervention or control group in a 1:1 ratio after the participant has given informed consent and eligibility for trial participation has been confirmed.

The randomisation schedule will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by NCTU and held on a secure University of Nottingham server. Randomisation will be stratified by site and nicotine addiction.

Participants will be randomised by either site trial staff, including Clinical Research Network (CRN) staff, research nurses, research midwives or any local site staff delegated by the site PI (face-to-face consultation or remotely) or by central research team, including SIP researchers, administrators or any staff delegated by the CI (remotely) using the online randomisation system via a secure website developed and maintained by NCTU. Staff randomising participants will not be blinded to treatment allocation, as they will need to ensure participants in each group receive relevant treatment information and referral, if required. The referrals will be made to local smoking cessation services, such as specialist stop smoking services or GP surgeries, following local referral practices.

Central research team members who deliver trial interventions will not be blinded to treatment allocations. These staff will not be involved in data collection.

Central research team administrative staff who collect follow up data and will not deliver trial interventions, will be blinded to treatment allocations when selecting participants to call, and at the outset of any data collection conversations. They will not have access to any systems that reveal treatment allocation, nor will they communicate with site staff about participant treatment allocations. In follow up interviews, the order of the questions in the case report form (CRF) ensures that outcome data is collected first, before asking any questions about study interventions that may reveal the treatment allocation. There is a theoretical risk that researchers conducting follow up might remember treatment allocations of participants they have previously called at earlier follow up points resulting in them not being blinded at the start of a data collection call. However, in other similarly-sized studies, with large numbers of participants, this has not been encountered.

Health professionals providing other health care, including 'usual care' intensive stop smoking support will not be blinded or informed of participants' treatment allocations. This is relevant to advice on using NRT in lapses.

Participants will be aware of the intervention they receive; they will not receive detailed information about intervention(s) available to those allocated to the other trial arm.
The only people with access to unblinded trial outcome data during the study will be the DMC and the independent statistician.

The Chief Investigator, Trial Statistician and Health Economist will remain blinded to treatment allocation until after final database lock.

Maintenance of randomisation codes and procedures for breaking code

For the participant there is open randomisation so, in the event of an emergency, the treatment allocation will be known without the need for randomisation codes to be broken.

TRIAL/STUDY MANAGEMENT

Chief Investigator (CI) and Deputy Chief Investigator (DCI) will have joint responsibility for overall project implementation and management. Senior Trial Manger (NCTU) will oversee NCTU trial input. Researchers from the Nottingham SIP research group will secure ethical, HRA and R&D approvals, liaise with site trial staff for recruitment and run economic analyses. NCTU will oversee data management; database development including, implementation, maintenance and randomisation and statistical analyses.

The TMG will meet at least every 2 months and will be responsible for the day-to-day management of the trial; CI, DCI, Senior Trial Manager (NCTU) and the Trial Manager (or delegates) will attend all meetings with selected co-investigators and other staff attending as project implementation requires. The TMG will report to the TSC at their meetings.

The TSC, providing independent oversight of the trial on behalf of the trial sponsor, will include colleagues with patient and public involvement (PPI), smoking cessation and perinatal trials expertise and sponsor representatives.

A Data Monitoring Committee (DMC) will oversee trial safety, being primarily concerned with unexpected threats to foetal and maternal safety. It is clear that smoking in pregnancy causes substantial harm to both pregnant women and infants but, there is no evidence that NRT does so and this is why NRT is a standard treatment for pregnant women.

NRT is a licensed treatment which is routinely used in pregnancy and has well-documented, side effects which are insignificant compared to harm caused by smoking, as discussed in the Introduction section. As ***all*** participants experience usual care in which they may be offered NRT, it is not possible to learn more about the side effect profile of NRT products within this study. Consequently, the DMC will not try to do this but, will instead monitor appropriate data to prevent unexpected harms occurring.

The DMC will receive AE and SAE data, separated by trial arm, as described in the '*Adverse Events*' section. The DMC will similarly receive '*pregnancy-related*' trial outcome data to ensure that it is fully able to assess ongoing study safety from a materno-foetal perspective (see '*Assessment of safety*' section and will report to the TSC.

The DMC and TSC will meet in accordance with the oversight committee charters; usually every 6-12 months.

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: Planned start date is 1st October 2020 with a 4-year duration. The recruitment period for the trial is anticipated to be 30 months. The in-trial pilot runs for the first 9 months of the main trial recruitment period. Participant follow up will continue for a maximum of 38 weeks following the end of recruitment. However, recruitment progress and timelines will be monitored against projected recruitment and timelines and will be adjusted if necessary.

Participant Duration: Participants will be in the study from enrolment at, on average, around 12 weeks gestation, until childbirth. Post birth data collection can be collected up to 10 weeks after the estimated due date.

End of the Trial
This will be when the final post birth data is collected for the final participant, as described above. The Trial Manager will notify the REC the trial has ended and, a summary of the trial report will be provided within 12 months of this.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The Participant Information Sheet (PIS) is written at a 12-14-year old reading level, as assessed by the online Flesch Kincaid readability tool. As such, the PIS is accessible and appropriate for all mothers, regardless of their age. To minimise contamination, detailed and specific information sheets listing exact intervention procedures in each trial arm ('What happens next') will be distributed after randomisation.

Participant Identification

A screening questionnaire (either paper or electronic) will be used to identify women who are potentially eligible and interested to learn more about the study. The questionnaire will highlight women who are <25 weeks pregnant, have been referred for or have received or attended an appointment as part of standard antenatal care, smoke ≥5cpd, are interested in stop smoking support and are willing to consider using NRT. The screening questionnaire will be accompanied by a copy of the PIS (paper or electronic). Potentially eligible and interested women will be asked to give their contact details and consent to pass these to the research team. They will have the opportunity to discuss the study with a research team member, either in person, or over the telephone before they decide to enrol in the trial. Informed consent will be obtained and a full formal eligibility check will take place prior to any data collection and randomisation.

Posters will display information about the trial in relevant clinical areas, and will include a link to and/or Quick Response (QR) code for an electronic copy of the PIS, which women will be able to access on their smartphones and similar devices.

Hospital antenatal recruitment setting: In hospital ante-natal recruitment settings, the usual care team will identify potential participants from patient records using eligibility criteria (e.g. smoke ≥5 daily cigarettes) and will contact them by letter, telephone, email or text, sending a

PIS (paper copy or a QR code/link) and, where appropriate, a copy of the screening questionnaire prior to their 12- or 20-week antenatal ultrasound appointment. Women will be encouraged to read the PIS and, if they chose to complete the screening questionnaire, they will be asked to bring it to the appointment, where they will have the opportunity to discuss the trial with their usual care team member. In some clinical settings, the site trial staff may be a part of the usual care team; where they are not, only the care team will access personal data and invite potential participants to the study.

Alternatively, when women attend hospital for ultrasound or other antenatal appointments, usual care may approach potential participants and ask them to complete the screening questionnaire (paper or online) to identify potentially eligible women. Additionally, if women have not been sent a PIS prior to their appointment or do not recall having seen one, these will be made available to women too. Potentially eligible women who are interested will have the opportunity to discuss the study further with a research team member (see '*Participant recruitment*', below).

Participant identification centres (PICs) in hospital antenatal settings:
Potential participants will be identified and approached by the usual care team using the methods outlined above, provided with PIS and asked to complete the screening questionnaire and provide contact details, which will be passed to the central research team, who will contact them to discuss study enrolment.

Community midwives (usual care team) may also refer potential participants to the central research team/site trial team. When approaching potential participants, they may use a study poster, which includes a link/QR code to the PIS, or a paper PIS, to inform women about the study. Interested women will be asked to complete the screening questionnaire and provide contact details, which will be passed on to either the site research team or the central research team. Then, a research team member will contact potentially eligible women to discuss trial participation in more detail.
Stop Smoking Services (usual care team) may also identify potential participants. Pregnant women who smoke are referred to NHS Stop Smoking Services (SSS) for help with cessation. Before SSS cessation support begins, a SSS staff member will contact referred women to eligibility-screen them using questions outlined above. With their permission, SSS staff will send eligible, interested women's contact details to the site or central trial team.

If patient appointments are routinely via telephone or video consultation, these will be considered equal to face-to-face meetings for participant identification.

Online: This will not involve recruiting women via NHS settings. Google, Facebook or other social media/internet advertisements will be targeted at women who smoke and are pregnant. An embedded link within adverts will lead to a webpage giving information about the study, PIS and the screening questionnaire which they will be asked to complete (as above). Any potentially eligible women will be contacted by the central research team/site trial team.

If the potential participant identified via a PIC or online falls under one of the SNAP 3 Trial sites, their details may be passed on to that site's local trial team for recruitment (see below).

In *any* participant identification setting, whenever women's contact details are requested, it will be made clear that sharing these with the research team does not imply study participation and further consent will be required for this.

When completing the screening questionnaires, only potentially eligible women will be asked to provide their contact details. When completing these online, only those who meet the initial

criteria will be given the option to provide contact details, while non-eligible women will be directed to the final "thank you" page of the questionnaire. For non-eligible women, reason for failure to screen will be recorded. If a non-eligible woman accidentally provides her details on a paper questionnaire, these will be destroyed by site staff. For potentially eligible women, who provide their details, but later decide not to take part or reveal information that would make them not eligible, their details will be removed from the secure database immediately. For potentially eligible women who are not contactable, their details will be removed from the database within 4 weeks from questionnaire completion.

Participant recruitment

Participant identified in hospital antenatal recruitment settings:

After participant identification, recruitment will be done by the site trial staff. For women who have read and fully understand the PIS and the study procedures, researchers will obtain written consent before study procedures begin. However, this can only happen if the woman decides for herself that she has had sufficient time to make her decision and all questions about the study have been answered at that appointment. If potential participants need more time, they will be telephoned by a researcher at least 24 hours later to further discuss their participation. Consent will be obtained using any consent method (i.e. face to face or 'distanced') detailed in the Informed Consent section below.

Participants identified by community midwife, stop smoking services, hospital PIC settings, and online:

After receipt of contact details, the central research team will send an email and/or a text message to potential participants to arrange a convenient contact time. Messages will also include links/attachments to the PIS and a copy of the blank consent form. After at least 24hrs a central research team member will telephone potential participants, check that they have read and understood the PIS, explain study procedures, answer questions and, if women are interested, confirm their eligibility. Consent will be obtained using only one of the 'distanced' consent methods detailed in the Informed Consent section below.

Where a stop smoking service has been set up as a recruiting site, women identified in any PIC setting may be recruited by site trial staff in that stop smoking service.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision.

Eligibility criteria

Inclusion criteria

Women of any age who:

- are <25 weeks' gestation and have been referred for or have received or attended an appointment as part of standard antenatal care
- smoke ≥ 5 daily cigarettes
- willing to set a quit date and accept referral to SSS
- are willing to use NRT patch to try to stop smoking
- able to understand written and spoken English
- able to give consent

Exclusion criteria

- already in a cessation study
- contraindications to NRT including: severe cardiovascular disease, unstable angina, cardiac arrhythmias, recent cerebrovascular accident or TIA, chronic, generalized skin disorders or sensitivity to nicotine patches or major foetal anomalies
- Currently uses e-cigarette every day or more frequently

The final exclusion criteria is necessary as participants are required to record behaviours on English language questionnaires and, the intervention leaflet and website are in English. There are insufficient resources to translate these into all languages which might be encountered.

Expected duration of participant participation
Study participants will be in the study from enrolment at, on average, around 12 weeks gestation, until childbirth.

Removal of participants from therapy or assessments / Participant Withdrawal
Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. They will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Loss to follow up will not be considered withdrawal and if participants request that one or more intervention components are discontinued, this will be considered treatment discontinuation, not a withdrawal request and they will be followed up. Study withdrawal will only be considered to have occurred when participants specifically ask to be withdrawn from all further study procedures. Whilst no attempt will be made to coerce participants to remain in the study, should a participant request withdrawal, a researcher will discuss this with them to ascertain which aspects of study participation are problematic. It may be possible, for example, to discontinue some treatment components without necessitating full study withdrawal. In any conversation about withdrawal, continued permission to use medical records data at the end of pregnancy and reasons for withdrawal will be sought.

Enrolled participants who withdraw before randomisation can be replaced but will keep their trial ID. Participants who withdraw after randomisation will not be replaced.

Informed consent

Informed consent will be collected from each participant before they undergo any interventions (including history taking) related to the study. Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form will be obtained from the participant, using methods described below.

During the pilot phase of the trial, both potentially eligible women who either do or do not consent to join the study will be invited to take part in an interview to determine their reasons and those who are interested will be sent a blank copy of an interview-specific consent form and PIS which describes this in more detail. They will be contacted via the telephone by central research team member, at least 24 hours later. If they are satisfied that they had sufficient time to read and understand the PIS, the researcher will collect their consent and conduct the interview. If not, they will be called again at an arranged time.

Methods of consent collection in different settings:

The Investigator, or delegate (as documented and authorised on the delegation of responsibilities), will obtain informed consent in each of the following scenarios, while adhering to local practices. Informed consent may be obtained **face to face** in the antenatal hospital recruitment settings. For women recruited by community midwives, in antenatal PIC settings and online consent may be obtained using '**distanced'** methods**,** such as by **telephone or**

video call. Women recruited in antenatal hospital recruitment settings who choose to delay consent (e.g. to have more time to decide) may also give distanced consent.

1. ***Face to face consent, collected in antenatal hospital recruitment settings*:** Signed informed consent will be obtained, using either a traditional **pen/paper consent form** or **electronic form (e-consent)**.

- **Pen/paper consent:** The participant will complete the form by initialling boxes to indicate agreement with each consent item (yes/no for optional items) The researcher will talk them through each consent item and answer any questions they may have. The researcher will countersign the form. One copy of the signed consent form will be given to the participant and the original will be stored by the central research team in a secure location. Further copies will be filed in the patient's medical records and Investigator Site File (ISF). The site trial staff will scan the paper form and onto the secure study database.
- **E-consent** in a face to face setting: women will also be provided with a blank consent form, to familiarise themselves with the consent items. They will then be asked to complete an online consent form as above and sign the online form using a finger/stylus/mouse on a tablet/phone/computer. The researcher will talk them through each consent item and answer any questions they may have. The details of the researcher taking consent will be logged within the online system. A PDF copy of the completed form will then be sent to the participant and another copy will be stored electronically by the research team. Further copies will be filed in the patient's medical records and ISF.

2. **Distanced consent collected over the telephone or video call:** Potential participants identified by community midwives, antenatal PIC settings and online, as well as those identified in hospital recruitment settings, who chose to delay consent taking, will be able to give distanced consent. In the first instance **e-consent** will be sought as the preferred method. Alternatively, if this is not possible, for example due to internet access restrictions, **verbal telephone consent** will be obtained. As stated in section "Participant recruitment" above, each participant will receive a copy of the PIS and a non-modifiable blank consent form, at least 24 hours before the consent call.

- **E-consent:** Women will be sent a link to an online consent form. During the call, they will be asked to complete the online form as described above, while the researcher talks through each point and answers questions. They will then sign the online form as above. The details of the researcher taking consent will be logged within the online system.

- **Verbal telephone consent:** Only if e-consent is not possible, for example due to lack of internet access, verbal telephone consent will be obtained, following a strict scripted protocol. During the consent call, potential participants will be asked to give explicit verbal agreement to the same statements as appear on the online or 'hard copy' of the consent form. The researcher will mark each item on the form as agreed by the participant. The details of the researcher taking consent will be logged within the online system. The researcher will tick a box to indicate consent was obtained verbally over the telephone.

A PDF copy of the completed form will then be sent to the participant and another copy will be stored electronically by the research team. A further copy will be filed in the patient's medical records. If the participant has been randomised to a specific site, a copy will also be filed in the ISF.

All participants will be asked to provide the contact details of their GP, and if recruited online, also of the hospital in which they intend to deliver their baby. For all methods of consent, a letter will be sent to the participant's GP informing them about study enrolment. GPs will be asked to contact the research team if they have any questions or to let the research team know if there is any reason why a participant is unsuitable for the study. For all women recruited online, GPs will be asked to let the researchers know if the woman is not registered at their practice, so that further clarification of the correct GP can be sought. For women recruited online researchers will also contact the hospital, to inform them about study enrolment and to explain that requests will be made for maternal/birth outcomes at the end of pregnancy. Women will be informed about this in the PIS and will be asked to give consent for this.

Interviews: For women who agree to take part in the interviews, distanced consent will be obtained by the central researcher as above. They will be asked to either sign an e-consent form or give verbal telephone consent (as described above) at the start of the interview call, before recording equipment is switched on.

Justification for telephone consent: The telephone consent process is commensurate with a small risk associated with using nicotine in pregnancy being substantially outweighed by the benefits of smoking cessation and reduced exposure to tobacco smoke from using NRT. NRT has been recommended in pregnancy by NICE since 2010[31] and eliminates the numerous poisons and carcinogens in tobacco smoke by exposing users solely to nicotine (see 'Background' for more detail). Additionally, study NRT is dispatched to women after randomisation, taking at least two days to arrive so, women will have this extra time to decide whether or not they will use NRT offered and sent to them as a pragmatic intervention component. Not allowing this option may be a barrier to recruitment, only allowing women with access to appropriate technologies to access this research opportunity. For each participant, a GP and/or hospital will be contacted, which will help verify their identity.

Under 16s: In accordance with the law, medical treatment can be offered to a young person, with their sole consent, if they are competent to give it. This is particularly relevant and commonplace in maternity settings, where mothers under the age of 16 provide consent for their care throughout pregnancy. The person taking consent must be confident that the mother under 16 is able to understand the nature, purpose and possible consequences of trial participation. They can then provide consent if they are judged as able to understand, retain, use and weigh this information, and communicate their decision to others (this is defined as being 'Gillick Competent').

The person taking consent must make sure that all relevant information has been provided and thoroughly discussed before deciding whether or not the mother has the capacity to consent, regardless of the mothers' age. An under-16 consenting mother should be encouraged to involve their parent(s) or guardians, another member of their medical team, or an independent advocate if that would help them in making the decision about participation. If the person taking consent has any concerns about a young person's capacity to understand study procedures or to give informed consent, the default will be to exclude them from the study. Staff taking consent will be trained in the specific considerations needed when assessing Gillick competence.

TRIAL / STUDY TREATMENT AND REGIMEN

STUDY INTERVENTIONS

There are no restrictions on other treatments which can be used by trial participants in either group, other than those constraints which operate in the delivery of usual clinical care.

Usual care

This is '*Very Brief Smoking Advice on Smoking for pregnant women*' (VBA) as defined by the National Centre for Smoking Cessation Training (NCSCT)[39], which comprises (1) carbon monoxide (CO) testing, (2) advice that intensive behavioural support enhances success with quitting and (3) referral for this, if available locally. A standard smoking cessation leaflet as a component of VBA will be provided.

Intensive behavioural cessation support is delivered by specialist practitioners, usually working for local authority SSS or the NHS. Content of support varies across the NHS[40] but there are three key ingredients:

i) help setting a quit date
ii) counselling, delivered face-to-face or remotely in telephone or video calls
iii) an offer of NRT, starting on a quit date (QD) when abstinence from smoking begins.[32 41]

NRT is only used for cessation and not to cut down smoking. There is no specific NHS guidance on whether pregnant 'quitters' who experience brief smoking lapses should continue or stop NRT.

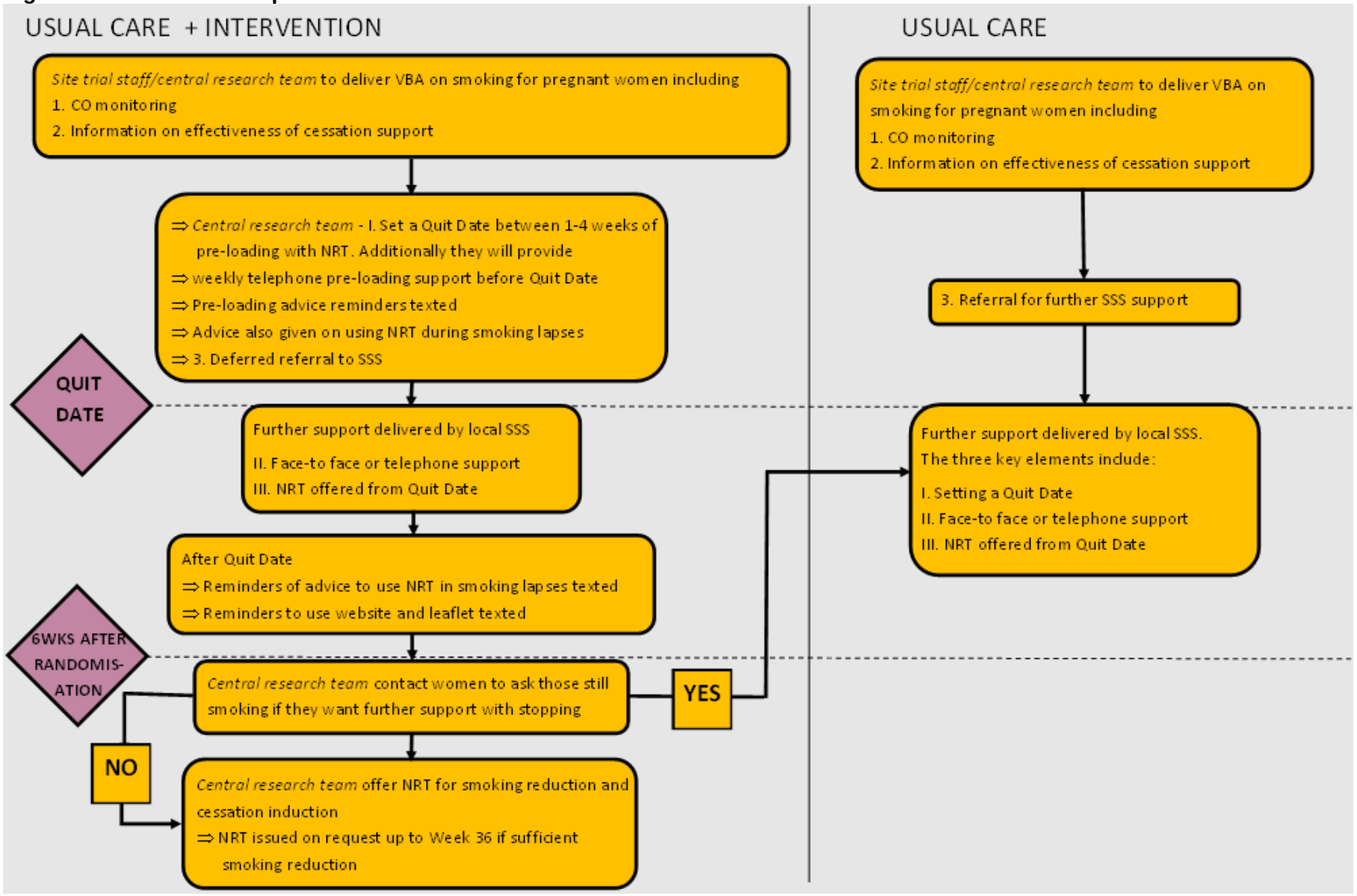
Where intensive behavioural support is available and provided by a specialist stop smoking service, women will be referred for this, arranging an appointment, if possible. Where no such support service is available, participants will be referred to their GP. Whether or not intensive behavioural support is available from the local NHS, a letter will be sent to participants' GP informing them that the participant is enrolled in a smoking cessation study. The letter will ask GPs to consider providing NRT, with the aim of helping them to stop smoking as per current NICE guidance, to any participants who consult with them. For participants recruited online, their home address postcode will be used to establish their locality and identify local stop smoking services. Participants will be referred for smoking cessation support to local stop smoking services by the central research team member, following local referral procedures.

Intervention
In addition to usual care, advice and support suggesting use of NRT will be provided in *three* ways (see Figure 1, below).

1 ***Preloading***
This is delivered before women's quit date and usual smoking cessation support begins and will be a pregnancy-specific version of support used in the Preloading Study, a recent NHS RCT.[20] Counselling will address any concerns about NRT or nicotine and instruct women how to use nicotine patches successfully and avoid side effects. Women will be asked to set a QD for between one and four weeks. In the interim, they will be asked to smoke less and wear NRT patches (15mg/16hr), changing these daily. After the initial preloading counselling session, participants will receive weekly telephone or video support calls, as required (maximum of 4) and will be offered additional NRT for up to 4 weeks.

A leaflet, simple text messages and website will reinforce counselling messages. Usual Care smoking cessation treatment will begin when Preloading is completed. If specialist, stop smoking services are available, participants will be referred to these for Usual Care intensive behavioural support, arranging their initial appointments, if possible. Where such services are not available, as per the Usual Care intervention, women will be referred to their GP for NHS support with smoking cessation.

Figure 1 Relationship of interventions and usual care



2 Advice to continue NRT in brief smoking lapses

Intervention group participants will be provided with advice about how to use NRT for quitting which differs from that given as part of routine care. They will also receive specific support through written materials, text messages and via a website to reinforce this advice-based intervention component. NRT used after the quit date will be supplied as usual care, rather than by the central research team.

Definitions
The first brief lapses in quit attempts are minor; in 70%[42] to 73%[43], quitters smoke only part of a cigarette; hence, we define:

- a 'brief lapse' as any smoking, even one puff, during an abstinence period which follows a quit date.

A brief lapse may develop into a 'relapse' when a 'quitter' fully returns to smoking; on average, this happens 19 days after the first lapse[42] so, we define:

- a relapse as any smoking, even a puff, on 14 or more consecutive days during an abstinence period which follows a quit date ***or*** if, during this period, they smoke > 5 daily cigarettes for 3 or more days.[42]

Advice
Advice will first be given in 'preloading' telephone or video call follow-up sessions delivered *before* participants' QD, and *after the QD,* the '*don't stop NRT when you lapse*' message will be reinforced by a leaflet (SSS-branded, if possible), a website and reminder texts sent.

Participants will be informed that, if they use NRT, achieve abstinence and experience a brief lapse, they should ***not stop*** NRT but they should ***continue*** this and keep on trying to stop smoking. If a relapse occurs, women should end the quit attempt and ***stop*** NRT; if they still want to try stopping, they will be asked to discuss a new quit attempt with local providers of 'usual care' NHS cessation support.

3 NRT to reduce smoking and induce cessation
At '*Follow up*' 1, it will be identified which participants are eligible to be offered this intervention component (details below). These women will be smoking and may have:

- made no attempt to stop
- tried to stop but failed
- accepted or declined referral for intensive behavioural cessation support earlier in pregnancy

Before offering this intervention, it will first be offered to re-refer these women for 'usual care' support to help them stop smoking. This intervention component will only be offered if they decline referral.

Women will be encouraged to use NRT to cut down smoking. A choice between 15mg/16hr NRT patches or 15mg NRT inhalator cartridges (maximum of 12 daily) will be offered and the possibility of swapping products if the first choice is not tolerated. Patch will provide a slow-acting, non-modifiable nicotine supply and inhalator, a fast-acting nicotine one, with

potential for participants to vary nicotine dose. Women will be asked to smoke fewer daily cigarettes than at enrolment and to use NRT instead of smoking some daily cigarettes. Additionally, they will be expected to reduce to smoking < 10 daily cigarettes as infants' birthweight reductions are greatest below this smoking intensity.[44] The '*use NRT to reduce smoking*' message will be reinforced by a leaflet, website and text messages.

At fortnightly intervals, provided women request it and, potentially until childbirth, 2-week NRT supplies will be offered to women who report smoking < 10 daily cigarettes and fewer daily cigarettes than at baseline. If either criterion is not met, NRT will still be supplied; however, in two weeks, at the next consultation in two weeks, unless both are met, no further NRT will be issued.

Self-monitoring smoking behaviour and NRT use: To allow women to self-monitor smoking behaviour and use of NRT, they will be asked to record this daily on a smartphone app called MyNRT From experience in similar trials, the majority of women own a smartphone, however women will not be excluded from this trial if they do not own a smartphone. In this instance, the MyNRT' app is not being used as a data collection tool, but a self-motivating tool for women to use during the reduction phase. MyNRT' app use will be recorded. For each day that they use NRT to reduce smoking and induce cessation, they will be asked to enter i) smoking status and ii) use of NRT or e-cigarettes. If smoking, they will be asked to enter the daily number of cigarettes smoked and, if NRT is used, they will be asked about the type and dose. If women are still using NRT to reduce smoking and so, a prompt is appropriate, after any 48 hr period of non-completion text message reminders will ask women to re-start using the app. No personal data is stored on MyNRT which sends pseudo anonymised data to Amazon cloud. A portal permits participants' data to be interrogated in real-time hence, staff delivering interventions will have access to data on women's reported smoking intensity during intervention consultations.

Staff delivering interventions

Usual care: In *hospital ante natal recruitment settings*, where *face-to-face recruitment* occurs, *VBA*, including referral for intensive behavioural support will be delivered by *site trial staff*. For participants consented by telephone, this will be delivered by central research team staff. To ensure fidelity in VBA delivery, those delivering this will be required to complete a checklist covering key VBA components, before they can progress through later parts of the CRF.

Intensive behavioural support for cessation, provided as usual care after referral, will be delivered by stop smoking practitioners employed by local authorities or within NHS maternity healthcare settings.

Intervention components

Interventions are delivered remotely by central research team staff. The researchers delivering interventions will need to pass appropriate NCSCT online training modules which, depending on their role, could include "Very Brief Advice on smoking for pregnant women" and/or "NCSCT specialty module: pregnancy and post-partum". They will also undergo additional trial-specific training, covering NRT use for pre-loading, lapse recovery and reduction. This training will highlight how the trial intervention varies from usual support for smoking cessation in pregnancy, and will be delivered either remotely or face to face, COVID-19 restrictions permitting.

1 *Preloading:* Following consent, central research staff will deliver brief, preloading-specific counselling support as soon as possible after randomisation. To ensure fidelity in preloading counselling delivery, those delivering this will complete a checklist showing key

components of this intervention are delivered before they can progress further into the CRF. central research team will make all follow up support calls.

2 *Advice on lapses* and *NRT for cutting down* will be delivered by central research staff in telephone or video calls.

STUDY DATA COLLECTION

Preventing distress

Women who have miscarried will not be routinely excluded from follow up but, attempt will be made to minimise any distress. A text reminder will be sent to participants the day before follow up is due with an option to respond and cancel this if they are too distressed to be called. Additionally the central trial office will send the site trial staff a list of participants being followed up within the next fortnight asking them to identify any participants for whom they consider follow up is likely to be too distressing; this view will be considered when deciding whether or not to follow up.

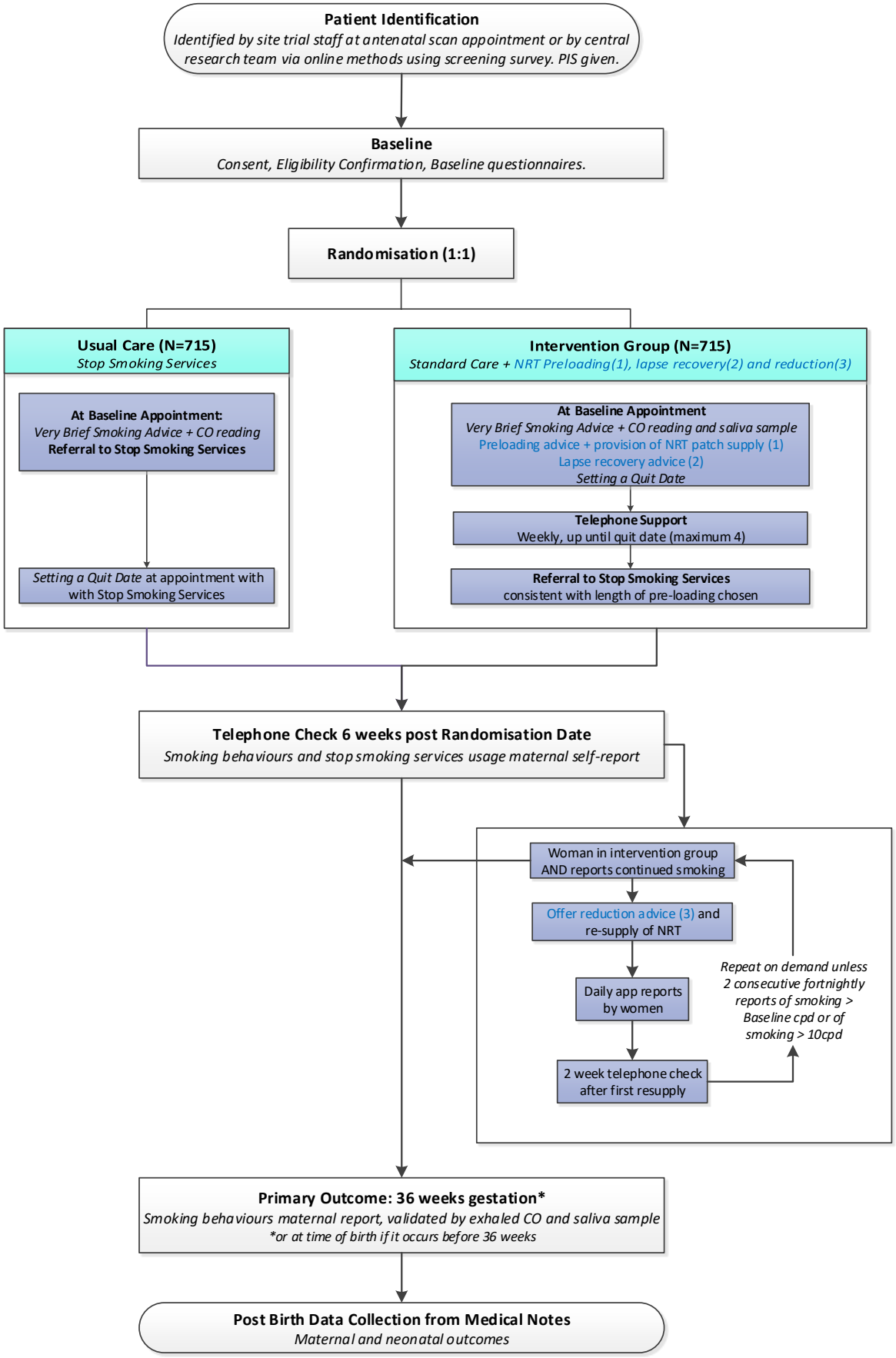
Table 2 shows all participant study assessments. Figure 2 gives an overview of the study design and data collection timepoints.

Table 2: Schedule of participant assessments and interventions

Participant Assessments	Pre baseline	Baseline	Before quit date (QD)	Follow Up 1: Randomisation + 6 weeks	Follow Up 2: Week 36 gestation or childbirth if earlier
Screening & consent	X				
Eligibility assessment	X				
Smoking behaviours		X		X	X
Nicotine dependence		X			
Saliva sample		X*			X
CO reading		X*			X
Randomisation		X			
Very Brief Advice for smoking cessation		X			
Stop smoking service usage				X	X
NRT use				X	X
Adverse events				X	X
Birth & maternal outcomes					X
Interventions delivered					
Pre-QD telephone behavioural support			X		
Supply of NRT for preloading offered			X		
Supply of NRT and telephone support for cutting down smoking offered				← →	
Use <App Name> App for self-monitoring smoking behaviour and NRT use				← →	

*Saliva sample and CO reading at baseline will be obtained from participants recruited in face to face settings only

Figure 2 Study Flowchart



Baseline data collection:

Baseline questionnaire: After obtaining *face-to-face* consent site trial staff will ask participants about socio-demographics; smoking beliefs and behaviour, gestation, nicotine dependence[45], urges to smoke, number of births beyond 24 weeks and partners' or significant others' smoking status. Following telephone consent, central research staff will ask for these data.

Sample collection: participants may be asked to provide a saliva sample, for cotinine assays, using clean salivettes, and potentially, depending on Covid-19 restrictions, an expired air CO reading, to indicate heaviness of smoking.

For participants consented face to face in antenatal hospital recruitment settings, when possible, saliva samples and exhaled air CO samples will be collected by the site trial staff. The staff will return the saliva sample directly back to the laboratory, via post. Exhaled air CO reading will be obtained using a standard hand-held CO monitor.

If samples are required from participants consented by telephone, or remotely, or at any time after baseline, saliva self-collection kits and / or 'individual-use' CO (iCO) monitors may be posted out. Women will return saliva samples to the laboratory by post. Those who receive iCO monitors will be instructed to download and use a smartphone app through which CO readings will be sent directly to the research team. Women will be instructed to keep the iCO monitor for sending future CO readings. There will be no third-party storage of participants' data by the iCO app. All equipment will be CE marked and used within its intended purpose.

Follow up data collection

Where appropriate, data will be first sought via an online questionnaire, with central research team staff following up non-respondents by telephone, email, text message or postal questionnaire.

Day 7 of preloading intervention (intervention group only)**:** Participants will be asked how many cigarettes per day they are smoking and if they are using NRT for preloading; we may request a further saliva sample and / or CO reading.

Follow up 1: Randomisation plus 6 weeks

Follow up 1 questionnaire: Participants will be asked about smoking status and quitting behaviour, whether or not a quit date was set and, use of stop smoking support. Participants will also be asked if NRT patches were used before the quit date and, if so, how many. For women who report a quit attempt, it will be ascertained if they used NRT before the quit date or for quitting, whether a smoking lapse occurred and, if so, whether NRT was continued or stopped during this.

Where follow up is by telephone, items on smoking behaviour will be asked prior to those about treatment. The question order will be determined by the CRF. This will prevent researchers from becoming aware of treatment allocations before asking about smoking outcomes.

Prompt to offer of third intervention component: At completion of follow up, if an intervention group participant reports smoking a database alert will inform the researcher team. If follow up is by telephone, researchers will advise them that they could be eligible for the third intervention component and, will arrange an appointment for them to discuss this further with a researcher. If follow up is not by telephone, the research team will contact women by telephone to explain this.

Intervention group only, within participants who accept smoking reduction intervention: At around week 8 – 12 post randomisation, we may ask for a saliva and / or an exhaled air CO sample; prior to sample collection we will confirm whether or not NRT is being used. Participants will be asked how many cigarettes per day they are smoking.

Follow up 2: 36 weeks gestation or childbirth, if earlier

Follow up 2 questionnaire: Participants will be asked about smoking and e-cigarette use, and about relevant cost data (*see next section*). Where smoking data are missing after data collection methods have been exhausted, staff in recruitment sites will obtain hospital 'Smoking at Delivery' data, with CO-validation, where available.[46]

After childbirth, *site trial staff* or *usual care staff* will extract maternal and foetal pregnancy outcome data from medical records and data on any infant admission to special care, congenital abnormalities, maternal and neonatal death. For participants, who were not recruited by site trial staff, including online recruits, their hospital care team will be contacted and asked to provide these data.

Validation of Smoking Status: 36 weeks gestation or childbirth, if earlier

The aim will be to validate reports of 7-day abstinence made at final follow up, using saliva cotinine or anabasine and CO. The latter two measures are used in women who report using NRT or e-cigs. Samples will be collected as women attend hospital, by post or, if necessary, via domestic visits. Domestic visits will be carried out by site staff, only if local arrangements allow this. Where necessary, saliva sampling or CO meters will be posted to women as per the baseline visit. Participants will be asked to report their smoking status and recent use of nicotine replacement therapies and e-cigarettes when they provide samples.

Incentives for follow up completion: Women will be offered £5 high street shopping voucher for completing each of the 6 weeks post-randomisation - and 36th week of gestation questionnaires; for providing a CO reading and/or saliva sample women will be offered an additional £20 voucher. Only women who report quitting will be asked to provide saliva sample. The voucher will be offered to women who provide a sample, regardless of the result of sample analysis.

***Costs of intervention delivery*:** Principal intervention costs will be identified and monitored, including both intervention delivery and staff training. Training costs will be estimated by multiplying staff time by hourly wage and will include both those attending as well as those delivering the training. Intervention costs will include staff costs (time spent counselling patient multiplied by hourly wage, prescription costs (number of prescriptions for NRT multiplied by BNF price), and material costs (number of leaflets multiplied by price of leaflet). This will be estimated for each arm of the intervention. For the NRT to reduce smoking and induce cessation arm, additional costs for text message support (cost of individual text message multiplied by number of text messages sent), and software will be included. At 36-weeks, participants will be asked about use of NHS SSS support or NRT received from other NHS sources (e.g. GPs, pharmacists, etc). Reported SSS will be triangulated with available SSS records, to estimate costs of participants' SSS support.

Qualitative sub-study to optimise recruitment

During the recruitment pilot phase, 28 potential participants will be selected from those who were asked to join the trial, including approximately 10 from each arm and, if possible, 5-8 who declined participation, for telephone interviews. Only women who completed the screening questionnaire, were potentially eligible to take part in the trial and gave consent to pass their details to the research team will be invited. Those selected will be sent a text message to inform them about possible further contact and will be send further information and consent forms which are specific to study interviews. Participants' and non-participants' interview topic guides will be designed and piloted, and semi-structured interviews will be

conducted by a central research team member, lasting up to 40 minutes, led by topic guides. Views will be sought on the acceptability of being offered participation, perceived barriers against and facilitators for (B&Fs) joining and whether the approach made to potential participants could be improved. Trial participants, will be also asked about acceptability of and concerns about intervention components. A conceptual framework of factors affecting recruitment for randomised controlled trials developed in past studies [47] will be used to support the design of the interview topic guides and to aid analysis. This framework encompasses factors such as participant/individual factors (e.g. motivation), study related factors (e.g. accessibility of study documents, technology related issues) and practitioner related factors (e.g. perceived communication skills, knowledge). Interviewees will be offered a £20 shopping voucher as compensation for their time. Interviews will be recorded; recordings will be sent securely to external transcribers who will produce anonymised transcripts. The University of Nottingham will sign a confidentiality agreement with the transcription service. Transcripts and recordings will be considered source data.

The trial qualitative lead will oversee a pragmatic, thematic analysis[48] using Nvivo 12 and supported by other team members as necessary. Although the conceptual framework [47] may be used to determine broad themes, inductive analysis will be conducted in order to capture barriers and facilitators specific to this population of participants and setting.

PPI co-applicants will bring lay insights to iterative data interpretation by commenting on appropriateness of emergent coding framework(s). Findings will inform improvements or modifications to recruitment, as appropriate and participants will not be identified in study reports.

***Process measures**:* To help interpret trial findings, using data from the above time points each trial arm will be quantified, the percentage of participants who use nicotine for preloading and, within participants who report lapses, the percentage who continue and discontinue NRT.

Compliance

This is a pragmatic study. Interventions are offered and although their adherence with these is monitored as study outcomes, no specific measures will be used to enhance compliance / adherence other than those described above.

Criteria for terminating trial

No interim analyses are planned and there are no formal 'stopping rules'; the DMC will periodically review and monitor accumulating data, making recommendations as appropriate. A review will be carried out by the TSC using the progression criteria outlined in Table 1, at the end of the trial pilot, to determine whether it is reasonable to progress to the full trial phase.

TRANSPORT AND STORAGE OF THE TISSUES

Saliva samples will be obtained from participants using clean salivettes. This will involve the participant placing a sterile swab under their tongue for up to 5 minutes, until it is moist, and then placing the swab into a sterile, labelled vessel. All samples will be labelled with the trial name, a unique participant identification number, visit number and the date of sampling. Samples will be stored in this format to permit accurate linkage to data and the consent form. All samples will be returned by post directly to the ACM Global Laboratories (using protective pre-paid and addressed packaging) on the day the sample is taken. Where participants are asked to provide saliva samples at home, they will be instructed to write the date they provided the sample on the label before returning to ACM Global laboratories by post as above. The samples will be tracked in two different ways; by the laboratory sending the research team weekly reports of all study samples received or by daily emails reporting every item time the laboratory log a saliva sample.

LABORATORY ANALYSES

ACM Global Laboratories will analyse all samples when required. The laboratory will quantify salivary cotinine and anabasine levels using a quantitative enzyme immunoassay technique (EIA). Once the analysis has been completed saliva samples will be destroyed in accordance with the Human Tissue Act 2004. This will be after the research team have received results, inspected these and all necessary sample retesting has been completed. The laboratory will provide confirmation once samples have been destroyed.

ACM Global Laboratories are a GLP accredited contract research organisation that specialises in the quantification of drugs, metabolites and biomarkers in biological and non-biological samples.

The contact for ACM Global Laboratories is as follows:

Osama Chahrour
Director of Bioanalysis
ACM Global Laboratories,
23 Hospital Fields Road, York
YO10 4DZ, UK
General tel: +44(0)1904 403600

STATISTICS

Methods

Trial analysis and reporting will be in accordance with CONSORT guidelines, with the primary comparative analyses being conducted according to randomised allocation with due emphasis on confidence intervals for between-arm comparisons. A full statistical analysis plan will be developed prior to completion of data collection and agreed with the Trial Steering Committee prior to database lock.

There are no planned formal interim analyses of treatment efficacy. Any analyses involving disaggregate data will be conducted by an independent statistician separate to the trial team.

Sample size and justification

SAMPLE SIZE

To detect a difference in smoking cessation in late pregnancy between control and intervention group proportions of 0.1 and 0.159 respectively (OR of 1.70) with 90% power and 5% two-sided alpha requires 715 participants per arm. There is no adjustment for missing data; it will be assumed those lost to follow up are smoking. Based on a recent SiP trial[49], assuming a quit rate in the usual care group of 10% and anticipate an odds ratio of 1.70 for the effects of NRT i) as preloading and ii) continued in smoking lapses to facilitate return to abstinence. An OR of 1.7 is considered clinically important and plausible, based on the anticipated effect of *preloading*[19 20] and *lapse prevention*[23 42 43] intervention components. The third intervention component (*NRT for smoking reduction*) will not contribute to the primary outcome as this is offered to participants who have returned to smoking.

Secondary outcomes: With 715 participants per group the study has 80% power to detect an 89g difference in mean birth weight, assuming a standard deviation of 600g[49]. The study also has 80% power to detect an absolute increase in the proportion of validated 7-day smoking abstinence at 36 weeks from 0.12 in the control group to 0.174 in the intervention group. Even if such magnitude of effects for birth weight are not apparent here, it is still important to report these data as, for other cessation interventions, meta-analyses have clearly demonstrated beneficial effects on birth outcomes.[4]

STATISTICAL ANALYSIS

Descriptive statistics of demographic and clinical measures will be used to assess balance between the randomised arms at baseline, but no formal statistical comparisons will be made. Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages.

The primary between-group analysis will use the intention-to-treat population, with those lost to follow up considered to be smoking. The primary outcome will be analysed using a mixed-effect logistic regression model adjusted for randomisation stratification variables with a random effect for site. The estimated between-group effect will be presented using both absolute and relative measures of effect, with associated 95% confidence intervals.

Maternal secondary outcomes will be analysed similarly, using appropriate regression models depending on the type of outcome variable and adjusting for randomisation stratification variables. Infant secondary outcomes will be analysed using appropriate regression models depending on the type of outcome variable, adjusting for randomisation stratification variables and accounting for correlation between outcomes for infants from multiple pregnancies.

Primary analysis will be repeated additionally, adjusting for any variables with marked imbalance at baseline.

Using appropriate interaction terms in the primary regression analyses for prolonged smoking cessation, it will be investigated whether treatment effectiveness differs according to the baseline level of nicotine dependence. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, this subgroup analysis will be regarded as exploratory.

Further exploratory analyses will be carried out for women in the intervention arm who are offered NRT for i) preloading and ii) smoking reduction; these will describe saliva cotinine and exhaled CO concentrations when smoking with those when i) preloading and ii) using NRT to reduce smoking. Another exploratory analysis will describe and compare the characteristics and outcomes of women who accept and do not accept NRT for smoking reduction and cessation induction. This will be first study of pregnant women to be offered NRT for smoking reduction as part of a trial.

Assessment of efficacy

For the primary outcome, number and percentage of participants achieving biochemically validated, prolonged abstinence from smoking reported between a quit date and 36 weeks gestation or childbirth, whichever is earlier, will be reported for each treatment group. For this outcome, smoking lapses are permitted during this period, provided no more than 5 cigarettes in total are smoked[38] and a 7-day period of total abstinence is reported immediately before primary outcome follow up.

Assessment of safety

Data for '*pregnancy related'* outcomes listed in the '*Secondary Endpoints*' section and adverse events, separated by trial arm, will be considered by the DMC. This will permit unexpected impacts on the pregnancy and foetus to be detected and responded to while the trial is ongoing. Although such impacts are unlikely, it is important to stay alert to this possibility.

These endpoints include pregnancy outcomes which are adversely affected by smoking which one would expect to improve if the study intervention reduces smoking and, also measures of smoking (CO) and of nicotine (cotinine) exposure. For a sub-group of intervention group women, longitudinal comparisons of both exposures (i.e. CO and cotinine) at baseline and when receiving study interventions will also be presented to the DMC. Hence the DMC will have sufficient information to decide whether trial interventions may be compromising foetal safety by being more harmful than smoking in pregnancy.

Procedures for missing, unused and spurious data

For the primary analysis of the primary outcome and for other smoking related secondary outcomes, participants with missing data will be considered to still be smoking; this is consistent with Russell Criteria which defines standard smoking cessation study outcomes[38] and has been proven a rational assumption in similar contexts.[50] However, sensitivity analyses may be conducted to make different assumptions to investigate the potential impact of missing smoking abstinence data.

Analyses of other secondary outcomes will use available data i.e. with no imputation for participants with missing data.

Definition of populations analysed

The primary analysis population will be all randomised participants and will follow intention-to-treat principles (i.e. analysed as randomised regardless of adherence with allocation).

Analysis of foetal loss outcomes will be conducted within all participants.

Analyses of birth outcomes (e.g. birth weight) will be conducted within all live births.

Adverse event data will be presented according to:

- randomised treatment group regardless of adherence with allocation and
- according to randomised group and NRT use

ECONOMIC ANALYSIS

NHS and Personal Social Services perspective[51] will be used with costs calculated at 2019-2020 prices for analyses using our published cohort model[52] which, with slight modification, has been adopted by NICE for an ongoing guideline update. It will be inputted into the model the trial cohort size; year; women's mean age and intervention costs and cessation rates. The model will extrapolate maternal and offspring smoking behaviours, estimating the impacts of this on healthcare costs and health-related quality of life. Estimates for incremental cost-effectiveness ratios (ICERs) per additional quitter, life year gained, and quality-adjusted life year (QALY), reported for the mother and offspring separately and combined, at end of pregnancy and across maternal and offspring lifetime horizons. To demonstrate return on investment, cost-offset ratios (CORs) defined as the difference in healthcare costs between intervention and control groups divided by increased costs of intervention delivery will be estimated. The model will also perform probabilistic sensitivity analyses and presenting ICERs, CORs, cost-effectiveness scatterplots and acceptability curves (CEAC) with 95% confidence intervals.

ADVERSE EVENTS

NRT is widely used both by pregnant and non-pregnant women who smoke. It has a well-documented safety profile which does not require further description and, known side effects are generally mild (see '*Known Side Effects*' section). Consequently, expected side effects from NRT which are listed in product SmPCs will not be considered Adverse Events.

Although, the study is of very low risk to participants and, in particular, the hazards of using NRT are well defined and compare very favourably with those from smoking, it is important to look for any unexpected effects of the intervention on pregnancy. Hence, the occurrence of serious events which could potentially, but would not necessarily, be expected to be caused by the intervention will be monitored, and the safety monitoring aims to differentiate such events from events caused by pregnancy itself.

Adverse event definition

Maternal hospital admissions for issues which are considered to be related to the underlying pregnancy are defined as ***adverse events*** **(AEs)** and need to be recorded as such; these will include admissions for:

- pre-term delivery before 32 weeks,
- low birth weight (< 2,500g),
- birth injury,
- infection,
- thrombosis,
- haemorrhage,
- hypertensive disease,
- instrumental delivery,
- caesarean section,
- pre-eclampsia or eclampsia and
- antenatal admissions for pregnancy related diseases such as false labour, infection, thrombosis, haemorrhage, hypertensive disease, suspected or confirmed foetal compromise, vaginal bleeding and for any other recognised pregnancy or postnatal complications.

Hospital admissions for other pregnancy-related gastrointestinal, respiratory, cardiac, renal skin, psychiatric and neurological problems are defined as adverse events.

Hospital admission for or following delivery where none of the above are present (i.e. normal childbirth) will be neither AE nor SAE.

Note: hospital admission for normal childbirth is a pre-planned or an expected admission and will not be considered as an adverse event. Hospital admissions differ from outcomes listed in the 'Secondary Outcomes' section (e.g. for premature birth, the study outcome is any premature birth but for this to be considered an AE, there needs to be a hospital admission or a prolongation of hospitalisation as a result of premature birth).

The following will be considered ***Serious Adverse Events*** (SAEs):

1 Maternal death

2 Maternal hospital admission or prolongation of existing hospitalisation for events which are ***not*** related to the underlying pregnancy or for a pregnancy related condition (see definition of Adverse Event above)

3 Maternal disability / incapacity where not related to the underlying pregnancy.

4 Congenital anomaly in the offspring of a participant

Events that do not require reporting as adverse events

The following are regarded as ***expected*** SAEs because they can occur in any pregnancy; for the purpose of trial and should ***not*** be reported on an SAE form.

- miscarriage
- stillbirth
- admission to special care
- 'hospital-recorded' neonatal death

These are serious events which are secondary outcomes and will be collected as part of the CRF/eCRF.

Causality

The following criteria will be considered when assessing SAE causality.

Not related or improbable: a clinical event with a temporal relationship to the trial treatment which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation will be counted as "unrelated" for notification purposes.

Possible: a clinical event with a temporal relationship to the trial treatment which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease will be counted as "related" for notification purposes.

Probable: a clinical event with a temporal relationship to the trial treatment which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease will be counted as "related" for notification purposes.

Definite: a clinical event with a temporal relationship to trial treatment which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes will be counted as "related" for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation. A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded in the e-CRF and closely monitored until resolution, stabilisation, or until it has been shown that the study intervention is not the cause. AE's will begin to be recorded from receipt of the study product by the participant until the end of the neonatal period.

The initial report must be made by the PI or delegate immediately (within 24 hours of being made aware of any SAE) by completing an SAE e-CRF form accessible via the web application. The PI will determine the seriousness and causality in conjunction with any treating medical practitioners. In addition, the SAE e-CRF form must be signed electronically within the web application by the PI or delegate. If for any reason the web application cannot be accessed, a paper SAE CRF form should be completed, scanned and emailed to the SIP team using the generic trial email address, marked for the attention of the CI. This inbox will be monitored daily (Monday to Friday). Staff should ensure that any patient identifiable information is not contained in any paper CRFs or documents when transferring forms. Any such information should be redacted.

The Chief Investigator or a nominated deputy shall be informed immediately of any serious adverse events and shall confirm categorisation of the event (this can only be an elevation in categorisation) Any change in categorisation will need to be countersigned by the PI.

AEs and SAEs will be reported in an annual safety report to REC and Sponsor.

DMC meetings will consider unblinded AE and SAE data and, if data indicates it appropriate, will recommend that individual AEs should be re-classified as SAEs, so that in-trial monitoring of such events is more rigorous.

Trial Treatment / Intervention Related SAEs

All **treatment-related** serious adverse events will be recorded and reported as part of annual reports. Unexpected serious adverse events deemed related to the trial intervention will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator or a delegate will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC within 7 days of knowledge of the event.
- Shall, within a further 8 days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2018 and Data Protection Act 2018.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. Informed consent must be obtained before the person can participant in the study.

The participant will receive a copy of the signed (where applicable) or otherwise documented and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of consent/study entry. The participant's date of birth (dd/mmm/yyyy) will be recorded in the database. The database will

be kept on a secure University of Nottingham platforms. Data on the server is regularly backed up, and access to both the server and database is password protected.

CRFs (paper and electronic) will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

Participants' name and contact details will be held in a separate confidential file at site, along with their identification number, to permit identification of all participants taking part in the study, in accordance with regulatory requirements and to allow follow-up as required. Access to CRFs and electronic databases (including access which permits new entries to be made) will be restricted to those personnel who are approved by the Chief or local Investigator and who are recorded as such in the study records. This will include any site trial staff involved in recruitment.

All paper forms (if used) shall be filled in using black ballpoint pen. Errors will be struck through but not obliterated by using correction fluid, and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling
Samples will be labelled with the assigned trial identity code number, the visit identifier (e.g. baseline) and the date the sample was taken.

Source documents
Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents
The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room and locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

No personal data will be stored on MyNRT app, which sends pseudo anonymised data to Amazon cloud. The researcher responsible for managing the MyNRT app for this trial is based at the University of Nottingham. Application Programming Interface (API) will be used to transfer the data from MyNRT to the University of Nottingham who are responsible for sending reminder texts, and a random security key will be required. MyNRT is PPI-tested and has been used in the previous studies; it is downloadable from Google Play and Apple Store.

Participants asked to provide a CO reading at home, using an iCO monitor, will be instructed to use a smartphone app in conjunction with the monitor, to send exhaled CO readings directly to the central trial team, with no third-party storage of participants' data.

Study related texts from the central research team will be sent by study researchers to organise data collection. The trial team may use the text carrier Esendex. Esendex will use participants' contact details to send text messages about the study. Esendex will hold contact details for no longer than 2 years. After this time, this information will be deleted. Full information security statement can be accessed here: https://www.esendex.co.uk/information-security-statement. Mobile phones supplied by the University of Nottingham will be used to text reminders and call participants for the completion of follow-up questionnaires.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Trial Manager/Monitor, or where required, a nominated designee of the Sponsor, shall carry out monitoring in accordance with the trial monitoring plan.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial

Manager/Monitor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity in accordance with the trial monitoring plan.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (as defined in the monitoring plan and based on risk assessment for the trial) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

We intend to write the results up for publication in peer reviewed journals and disseminate at local, national, and international meetings where appropriate. Papers describing the key findings will be submitted within 12 months of the trial completion. A lay summary will be

produced and distributed to those participants who have indicated they would like to receive a copy and other interested parties. Participants will not be identified in any publications or presentations resulting from this study.

USER AND PUBLIC INVOLVEMENT

Development of the study protocol

Dr Kasia Campbell (KC, co-applicant) co-ordinated all input from PPI informants.

Interviews with advisors: There are no specialist interest groups representing pregnant women who smoke. Previously, PPI advisors have been recruited from within those groups that are interested in pregnancy wellbeing (e.g. National Childbirth Trust); however, although such informants might have experienced pregnancy, they generally do not smoke or encounter material disadvantage associated with smoking in pregnancy. Hence, a low cost, quick method for recruiting PPI informants from Facebook adverts has been developed; and have largely recruited to and replenished the Smoking in Pregnancy (SiP) PPI group using such online methods.

For this study, the notion was discussed of using NRT in pregnancy i) as preloading, ii) in brief lapses and iii) to help cut down smoking with five PPI advisors who had smoked during their pregnancy. Of these, three were recruited via Facebook adverts and two were already SiP PPI group members. Three had stopped smoking in pregnancy (two with NRT and one with e-cigarettes), and two smoked throughout gestation. There was specific interest about their thoughts on the acceptability and feasibility of NRT used in these three ways.

All informants thought NRT preloading could work by reducing cravings and preparing women for using NRT alone, possibly also encouraging women to engage with SSS. Similarly, all felt using NRT during smoking lapses was more acceptable than potentially allowing these to result in a return to smoking and they could see how this could mean fewer women felt less “like failures” and how a return to abstinence could be quicker. In addition, informants thought that encouraging women who failed in quit attempts to cut down with NRT was better than them smoking as usual. However, there was some concern about allowing women to use NRT throughout pregnancy without any focus on abstinence. In response to this point, third intervention component was amended such that researchers will monitor participants’ heaviness of smoking and will stop NRT being stopped if women admit smoking more heavily than at baseline or > 10 daily cigarettes. This change was made to ensure a focus on reducing smoking when using NRT, rather than on ‘smoking as normal’; as it is believed this change enhances likely intervention acceptability.

PPI co-applicants

Two PPI co-applicant were recruited. One assisted the SiP team at the early stages of the application process, commenting on lay summaries. The second PPI co-applicant replaced the first person in the later stages of the application process, giving feedback on the final version of the protocol. The PPI co-applicant and two other PPI representatives assisted the SiP team with review of participant facing documents and trial processes prior to Ethics submission.

PPI involvement in study conduct

PPI co-ordinator and/or Trial Manager will lead study PPI. To ensure PPI involvement in the project’s strategic direction, two PPI representatives independent from the study team will be invited to attend each TSC meeting. Additionally, a PPI representative will be invited to attend or contribute to any TMG meetings where the research team, including PPI advisors,

consider lay opinion is likely to be of value, their time will be used well and any meeting attendance would not be tokenistic. New PPI advisors may be recruited, as necessary via Facebook advertising, PPI Facebook groups, SiP PPI group or a Nottingham based 'Smoker's Panel' run by SPECTRUM (formerly, UK Centre for Tobacco and Alcohol Studies)

The SIP PPI group will be consulted for their opinion on any aspects of study conduct, which the research team, including PPI co-applicants, believe is important and relevant. This will likely include but is not exclusive to:

- Methods for identifying, approaching and recruiting participants to the RCT and qualitative sub-study
- Methods for follow-up contact with participants
- Preparing ethics applications
- Design of study materials, such as participant letters, questionnaires, interview topic guides etc.

STUDY FINANCES

Funding source

This study is funded by NIHR HTA.

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Participant stipends and payments

Participants will not be paid to participate in the trial. To recognise time taken in complying with study procedures, women will be offered £5 in high street shopping vouchers for completing each of the Week 6-post randomisation (FU1) and 36th week of gestation (FU2) questionnaires; for providing a CO reading and/or saliva sample at the end of the study, an additional £20 voucher will be offered.

During the in-trial pilot, participants in the intervention group who preload NRT will also receive £20 shopping vouchers for providing a saliva/CO sample while using NRT for pre-loading prior to their quit date; participants who accept the 3rd component of the intervention will receive £20 shopping voucher if they provide saliva/CO sample when using NRT for smoking reduction.

Participants who take part in interviews for the qualitative sub-study to optimise recruitment will also receive £20 shopping voucher.

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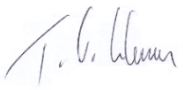
SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Prof Tim Coleman

Signature: 

Date: 3rd March 2022

Co- investigator/Principal Investigator:

(name) _____

Signature:_____

Date: _____

Trial Statistician: Lucy Bradshaw

Signature:_ 

Date: 7th March 2022

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