STUDY PROTOCOL

1.0 Title Page

Full/Long Title

Helping Pregnant Smokers Quit: A Multi-Centre RCT of Electronic Cigarette and Nicotine Patches

Short Title and Acronym: Pregnancy Trial of E-cigarettes and Patches (PREP)

Sponsor

Queen Mary University of London

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REC Number 17/LO/0962

Sponsor Reference ReDA number 011822

IRAS Number: 220190

EudraCT Number: 2017-001237-65

ISRCTN Number: ISRCTN62025374

2.0 Signature Pages

Chief Investigator Declaration

I confirm that the following protocol (Version 4.0, dated 3/01/18) has been carefully reviewed by me and I, as the Chief Investigator, agree to conduct the trial in compliance with this version of the protocol.

I will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and all subsequent amendments of the clinical trial regulations, current Research Governance Framework, the World Medical Association Declaration of Helsinki (1996), GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publically available through publication and/or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator: Professor Robert Walton

Chief Investigator Site: Queen Mary University of London

Signature: ..... Robert Walton. .....

Date: .3...../..01..../..18....

Name (please print):

.....ROBERT WALTON.....

Statistician Declaration

The clinical study as detailed within this research protocol (Version 4.0 dated 3/01/18), involves the use of an investigational medicinal product and will be conducted in accordance with the current Research Governance Framework for Health & Social Care the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials, ICH E10 - Choice of Control Groups and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Statistician: *Irene Kaimi*

Job title: Senior Statistician

Statistician Site/Organisation: Barts Clinical Trials Unit, Queen Mary University of London

Signature: .....  .....

Date: 3/01/2018

Name (please print):...Irene...Kaimi.....

Principal Investigator

I, as Principal Investigator confirm that I have read and understood the following protocol (Version 4.0, dated 3/01/18). I agree to conduct the trial in compliance with this version of the protocol. I will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current Research Governance Framework, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

Principal Investigator Name:

Principal Investigator Site: *Please insert the Principal Investigator's Site.*

Signature:.....

Date: ...../...../.....

Name (please print):.....

This page must be signed by each PI at every site, and kept in the ISF, a copy of this page must be sent to the lead site/coordinating centre as evidence.

3.0 Key Trial Contacts

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Committees (DMEC, TSC, TMG)	TSC Chair: Dr Jamie Brown, UCL Nominated DMEC Chair: Prof Paul Aveyard, University of Oxford (to be agreed by HTA) .

4.0 Trial Summary

Full title	Helping pregnant smokers quit: Multi-centre RCT of electronic cigarettes and nicotine patches
Short title and/or Acronym	PREP
Trial Design Methodology	Randomised controlled trial
Phase of the Trial	IV
Study Duration	48 Months: 8m for trial set up; 26m for recruitment; 10m to complete remaining treatment and follow-ups (follow-up time-point after 4-week treatment will vary between 5 months-8 months + 1 month to allow follow up of non-responders); 4m for analysis and close-out. Expected start date is 1/5/2017. The planned end date of all clinical interventions is 30/5/2020. The planned end date of the whole trial is 30/4/2021.
Study setting	Recruitment: Multi-site – NHS Trial Co-ordinating centre: Health and Lifestyle Research Unit (HAL), QMUL.
Investigational Medicinal Product(s)	Nicotine Transdermal Patches
Medical condition or disease under investigation	Smoking/tobacco addiction
Planned Sample Size	1140
(Maximum) Treatment duration	8 weeks (4 weeks behavioural support + EC/NRT, and 4 further weeks of EC/NRT if requested).
Follow up duration	3 months post-partum
End of Trial definition	The study would be completed and the REC informed, 6 months after the final participant has been followed up for their 3m post-partum follow-up, to allow for saliva sample analysis to be completed.

5.0 Protocol Contributors

Key Protocol Contributors	Full contact details including phone, email and fax numbers
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6.0 List of Contents

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7.0 List of Abbreviations / Glossary of Terms

AE- Adverse Event
AR- Adverse Reaction
CI- Chief Investigator
CPD- Cigarettes Per Day
CRN- Clinical Research Network
CSO- Chief Scientists Office
CTU- Clinical Trials Unit
DMEC- Data Monitoring and Ethics Committee
EC- E-cigarette
e-CRF- Electronic Clinical Records Form
HAL- Health and Lifestyle Research Unit
IMP- Investigational Medicinal Product
ISF- Investigator Site File
JRMO- Joint Research Management Office
MHRA- Medicines and Healthcare products Regulatory Agency
NIHR- National Institute of Health Research
NRT- Nicotine Replacement Treatment
PI- Principal Investigator
PIS- Participant Information Sheet
QMUL- Queen Mary University of London
RCT- Randomised Controlled Trial
REC- Research Ethics Committee
RM- Research Midwife
RSI- Research Safety Information
SAE- Serious Adverse Event
SAR- Serious Adverse Reaction
SSS- Stop Smoking Services
SmPC- Summary of Product Characteristics
SOP- Standard Operating Procedure
SUSAR- Suspected Unexpected Serious Adverse Reaction
TQD- Target Quit Day
TMF- Trial Master File
TMG- Trial Management Group
TSC- Trial Steering Committee

8.0 Introduction

8.1 Background and study rationale

Smoking in pregnancy: Smoking in pregnancy is associated with increased risks of miscarriage, stillbirth, prematurity, low birth weight, perinatal morbidity and mortality, neo-natal and sudden infant death [1] and possibly also adverse infant behavioural outcomes [2, 3]. In the UK, the annual smoking-attributable maternal and infant health care costs are estimated at £20–£87.5 million [4]. As smoking in pregnancy remains highest amongst socially disadvantaged women [5], eliminating it could reduce socioeconomic inequalities in stillbirths and infant deaths [6]. There is systematic review-level evidence that when pregnant smokers successfully quit, infants' birth outcomes are improved [7] and it is very likely that other morbidities in both mothers and children will be substantially reduced following this crucial health behaviour change [1].

Interventions for pregnant smokers: Finding effective interventions that help pregnant smokers quit has remained elusive so far. Although around 50% of pregnant smokers try quitting [5], spontaneous quit rates in pregnant smokers in the UK are low [8]. Advice by health professionals combined with behavioural support and pharmacotherapy can provide some help, but the effect is limited [9-11]. NIHR and CSO funded several large RCTs to address this problem. An exercise intervention with multi-session behavioural support improved exercise levels but did not help with smoking cessation [12](7% of pregnant smokers achieved abstinence by the end of pregnancy). Financial incentives have shown promising results, but there are practical and ethical issues in applying this approach in routine care [10, 13]. A trial of nicotine patches [14, 15] provided reassuring data on the safety of nicotine replacement in pregnancy, but patches lacked efficacy (9% maintained abstinence to delivery). The two other smoking cessation medications, varenicline and bupropion, include labelling that cautions against use in pregnancy. EC appear to be the most promising of the remaining options, with a realistic chance of providing practical help to pregnant smokers and their children, but no study has tested them in this context so far.

Electronic cigarettes (EC): EC are used with increasing frequency by smokers wishing to limit or stop smoking [16]. EC allow self-titration of nicotine intake [17] and apart from nicotine, they also provide a degree of sensori-motor replacement and enjoyment [18]. This is the most likely explanation of the fact that EC are much more popular among smokers than NRT [16] and generate higher user ratings and better adherence [19].

EC do not contain most of the chemicals responsible for health risks of smoking and those that are present are there at levels much lower than in cigarette smoke [20]. A recent Cochrane review reported no safety concerns over EC use for up to 1.5 years [21]. Some dangers may yet emerge over long-term use, but taking such uncertainty into account, the overall risks are estimated to be some 95% lower than risks of smoking [20]. Although potential population effects of EC, such as a possibility that EC use may renormalize smoking, remain a matter of controversy, there is now a general consensus that EC have a potential to act as treatment for smokers who cannot stop smoking unaided. In cohort studies, promising proportions of hard-to-reach smokers given EC reduced or stopped smoking, including smokers unwilling to quit and smokers with schizophrenia [22-24]. Some UK Stop Smoking Services (SSS) are now using EC and report encouraging results [25, 26]. SSS monitoring data show that smokers using EC have higher cessation rates than smokers using other approaches [26]. Two randomised trials evaluated EC for smoking cessation so far. Both trials used obsolete EC products with low nicotine delivery and in addition, one trial used minimal support [19], while the other concerned smokers unwilling to quit [23]. Despite this, the Cochrane review analysing the trials concluded that EC are an effective treatment [21]. The conclusion is marked as tentative due to the small number of trials, but the uncertainty concerns the size of the effect rather than its direction because EC deliver nicotine and there is ample evidence that NRT is effective [27]. A recent review of reports that evaluated quitting in people who used EC in the past reported a negative result [28], but this was because smokers who were helped by EC have left this population (because they gave up smoking) and only those not helped have remained. Such studies say nothing useful about EC's effectiveness other than that they don't help everyone.

Despite being on the market for only a relatively short time, EC may already be having a population level impact. It is estimated that in the UK some 20,000 smokers are quitting with EC per year who would not have quit otherwise [16].

Use of EC in pregnancy: Pregnant smokers typically use NRT reluctantly, only when asked to do so by their health care providers, but some use EC spontaneously despite the fact that NRT is provided free on the NHS while EC have to be purchased [29, 30]. One of the co-applicants (Ussher) surveyed two London SSS over a period of 3 months and found that 25% of pregnant smokers were regularly using EC. In a small survey, a local pregnancy advisor asked ten consecutive pregnant smokers not using EC whether they would consider using EC as an aid to stop smoking. Seven would, two were not sure and one would not. A recent study based on focus groups with 87 pregnant women found that pregnant smokers perceive EC as safer than cigarettes [31]. Finally, Ussher is leading an ongoing CRUK study which involves interviewing pregnant and postpartum women about EC. Among 15 women interviewed so far, there is a consensus that EC are considered safer than, and are preferable to, smoking and that the women need more information about EC. A survey of 252 US obstetrician-gynaecologists found that the majority want to know more about the safety and efficacy of EC in pregnancy [32] and commentators have called for trials of efficacy and safety of EC in pregnancy including commentators with anti-EC stance [29, 30]. The results from these independent sources of information are consistent in suggesting that pregnant smokers are likely to be generally open to EC use, and that there is an urgent need for information on EC safety and efficacy in this group.

EC vs NRT in pregnancy: NRT has not shown efficacy in pregnancy, but there are reasons to expect that the barriers to NRT efficacy will be much less detrimental in the case of EC. Pregnant smokers seem to dislike oral NRT products but adherence to nicotine patch use is also very poor [14, 33] e.g. only 7% of women used patches for more than 1 month in the large UK trial [14]. Pregnant smokers may be finding patch use by itself unrewarding as the patches provide nicotine slowly without any immediate feedback or sensorimotor reinforcement. Interestingly, pregnant smokers seem to experience more severe cigarette withdrawal and cravings than other adults [34]. This could be related to stress and/or metabolic changes in pregnancy. Finally, pregnant women metabolise nicotine faster than other smokers and may need higher nicotine doses delivered at a faster rate than standard NRT formulations provide [35].

In contrast to NRT products, EC provide a degree of sensori-motor replacement for smoking and a degree of enjoyment [18]. They also allow extensive individualisation (of flavour, ease of use, and other product characteristics). Regarding nicotine delivery, EC remain inferior to cigarettes, but they deliver nicotine faster than nicotine patches and oral NRT products [36] and unlike patches, they allow for titration of nicotine intake to smokers' needs. These characteristics make it likely that pregnant smokers will adhere to EC treatment much better than to NRT treatment, possibly even magnifying this effect observed with other smokers (in the randomised trial comparing patches and EC, adherence to EC was over three times higher than adherence to patches – [19]). Pregnant smokers using EC are also likely to obtain more adequate nicotine replacement levels and withdrawal relief.

Despite being more palatable than NRT and providing better nicotine replacement, EC deliver lower levels of nicotine than cigarettes, do it much more slowly, and do not include other chemicals contributing to the addictiveness of cigarettes. Even enthusiastic EC users report much lower levels of dependence on EC than they experienced with cigarettes [37]. The National Centre for Smoking Cessation Training (NCSCT) midwifery guidance considers vaping (EC use) in pregnancy better than smoking [38].

In summary, there is a strong rationale for testing the efficacy of EC as a stop-smoking treatment for pregnant smokers. This is an important group for whom few practicable and effective interventions exist. EC have a theoretical potential to be of help and are already used by some pregnant smokers. Finding out whether EC do help is an important priority.

8.2 Assessment and management of risk

Safety of EC in pregnancy: A trial of EC in pregnancy raises safety concerns, which need to be addressed. Such concerns can be divided into concerns about safety of nicotine and safety of other EC ingredients.

Concerns about safety of nicotine in EC are the same as concerns about safety of nicotine in NRT. Pregnant smokers already consume nicotine from cigarettes at doses that are higher than those provided by NRT (and EC [20]). There is a consensus that NRT is much safer than smoking in pregnancy and NRT is universally used by UK pregnancy stop-smoking services [39]. In addition to this, the only RCT which has monitored infant outcomes after nicotine patch use in pregnancy has demonstrated better infant development at two years amongst children born to women randomised to NRT than those randomised to placebo [15], suggesting that nicotine may not in fact pose any major harm to the foetus. The smoking-attributable foetal harm is likely caused by products of tobacco combustion such as carbon monoxide and chemicals such as polycyclic aromatic hydrocarbons which are strongly associated with reduced foetal growth in utero [40] and which are virtually absent in both NRT and EC.

Regarding adverse effects of other chemicals in EC aerosol, the main components of EC liquid are propylene glycol, which is approved for use in pregnancy (e.g. in asthma inhalers) and glycerine, which has no known adverse effects, e.g. glycerine syrup not considered to pose risks in pregnancy. EC are used by millions of smokers and pose little risk over short-term use (up to 1.5 years) [21]. To our knowledge, no chemicals other than nicotine have been identified that would be inhaled by vapers (EC users) in quantities likely to affect the health of the foetus.

Users sometimes report coughing and one EC user was reported to develop transient lipoid pneumonia [41] which was attributed to glycerine-based oils in e-liquid. This is unlikely though, because glycerine is an alcohol and not a lipid. A coincidence is a more likely explanation as no other such cases were identified.

As with all lithium batteries, e.g. in mobile phones and laptops, instances were reported where EC batteries overheated or exploded. This was mostly with use of wrong chargers or DIY modifications. It is important that users receive adequate instructions on battery use and that the chargers are CE marked and compatible with the device used. (The proposed trial would use devices that comply with the latest British Standards and Electrical Equipment Safety Regulations). A trial of EC use in pregnancy would, of course, have to include close monitoring of all adverse events and also of pregnancy outcomes. We would use a similar approach to that applied in the study by Coleman et al [14] (see 'Pharmacovigilance' section for a detailed account of which adverse events will be monitored).

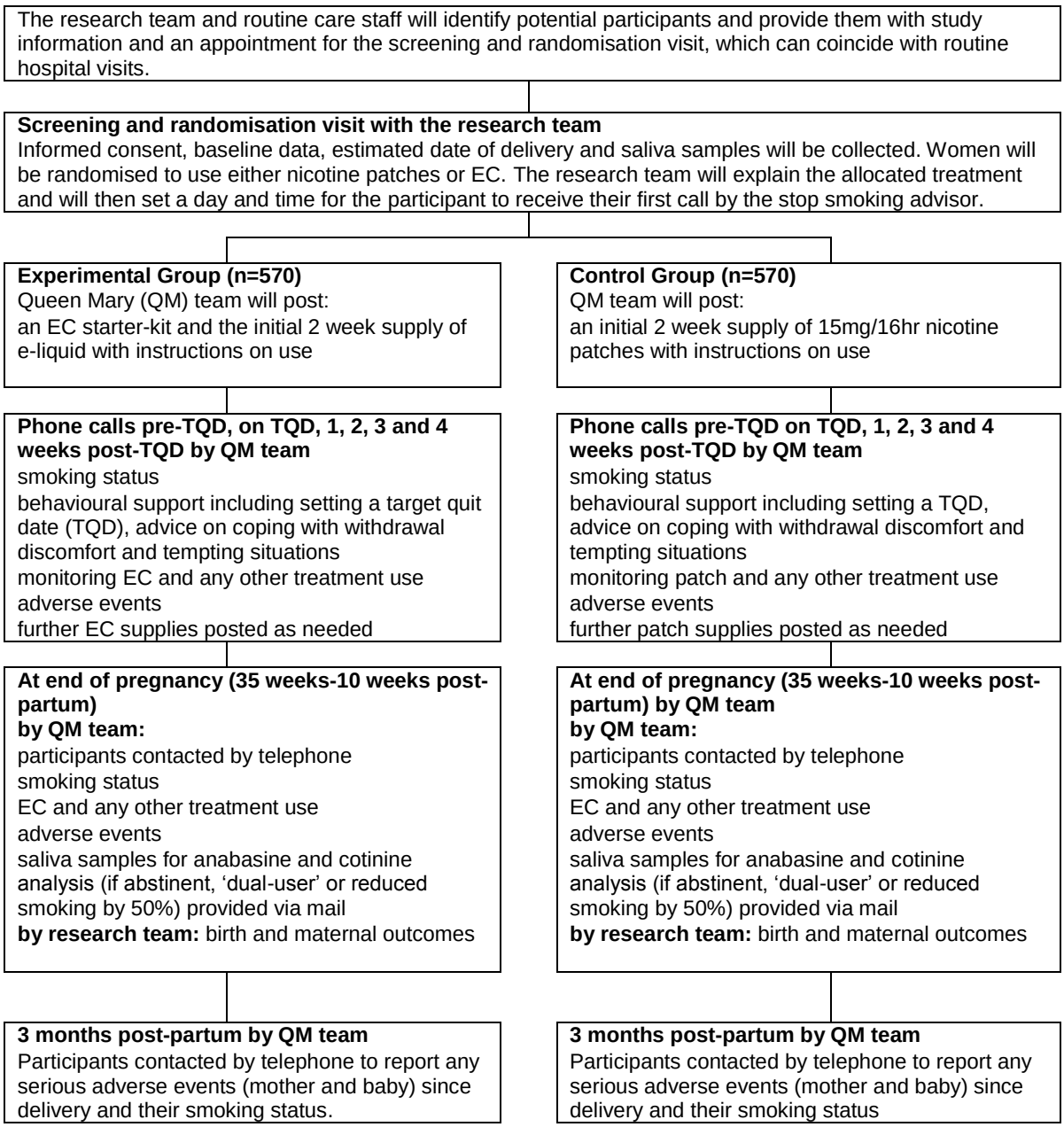
In summary, there are some safety concerns, particularly regarding nicotine, but they are tempered substantially by the fact that EC are not used de novo, but as a replacement for cigarettes and that cigarette smoke contains numerous other chemicals responsible for foetal harm and are vastly more risky on all counts, including the fire hazard. The trial would, of course, closely monitor any adverse events. It is highly unlikely that over short-term use EC would prove more harmful than NRT, but in the event of any unexpected harms, the trial would be stopped. Such a negative result would, in fact, be of significant value. EC are currently being used by an increasing proportion of pregnant smokers. If such use involves an unacceptable degree of risk, evidence of this would have important practical implications.

Safety of nicotine transdermal patches in pregnancy:
The points above regarding nicotine in pregnancy apply to use of nicotine patches in pregnancy as well. In the UK, nicotine skin patches are currently used routinely with pregnant smokers across the Stop-Smoking Specialist Services.

This trial has been categorised as a Type A, low risk Clinical Trial of an Investigational Medicinal Product (CTIMP) Nicotine patches constitute the IMP, and will be used on-label. The EC is a consumer product regulated under the Tobacco Products Directive (TPD). We will be providing a TPD-approved EC starter pack to participants (see intervention details), but they will be able to purchase a different EC and/or e-liquid if the

one provided does not work for them. This is the current approach by stop-smoking services (e.g. Leicestershire, Bristol and the City of London SSS) who provide EC starter packs as part of standard care and encourage clients to switch to other EC products if needed.

9.0 Trial Flowchart



10.0 Trial Objectives and Design

10.1 Primary Objective/s

To assess long-term (end of pregnancy) efficacy of electronic cigarettes (EC) compared to efficacy of nicotine transdermal patches when used to help pregnant smokers stop smoking.

10.2 Secondary Objective/s

To assess safety of electronic cigarettes (EC) compared to safety of nicotine transdermal patches when used to help pregnant smokers stop smoking; to assess effects of the two interventions on changes in smoke intake and in nicotine intake, effects on short-term abstinence; and adherence to each treatment.

10.3 Endpoints

10.3.1 Primary Endpoint

Prolonged abstinence from smoking from two weeks after the Target Quit Date (TQD) until the end of pregnancy defined as per Russell Standard (up to five lapses allowed with no smoking at all during the previous week at the time of final follow-up [42] and validated by salivary cotinine (< 15 ng/ml [42]) for those not reporting using any nicotine product and anabasine (< 1 ng/ml [43]) for those reporting other forms of nicotine use.

Many pregnant smokers who abstain during pregnancy return to smoking after the delivery. To collect data from the period when smoking is affecting the foetus and minimise the post-delivery relapse effect, we will make the first follow-up call at week 35. Given the likelihood that some women will only be reached after repeated attempts and that longer followed periods have generated high follow-up rates in the previous trials, we will allow a further ten week period to reach participants. If a participant is reached post-delivery, we will also record smoking status prior to the delivery.

10.3.2 Secondary Endpoints

Changes in smoke intake and in nicotine intake indexed by salivary anabasine and salivary cotinine levels, assessed for participants still using NRT or EC at end of pregnancy and for 'dual users' or those who have reduced their smoking by 50% or more; 7-day point-prevalence abstinence self-reported at 4 weeks, end of pregnancy and at 3 months post-partum; self-reported prolonged abstinence at end of pregnancy and 3 months post-partum; use of NRT and EC throughout pregnancy; proportion of participants reporting adverse events and serious adverse events in each group; proportion of participants in each group reporting adverse events and serious adverse events for themselves or their infant at 3 months post-partum; birth and maternal outcomes.

10.4 Exploratory or Tertiary endpoints/outcomes

Inclusion of longer-term outcomes:

We understand the need to plan for potential longer term follow up if an unexpected difference in birth outcomes emerges. Should this happen, we would apply (separately from this application) for additional funding to examine longer term outcomes for both mother and child but to prepare for this, we will undertake some early steps 'up front'. This will include ensuring that the informed consent allows us to use NHS mechanisms for finding out people's addresses or to use NHS numbers for women's and infant's follow up. Having adequate initial consent will ensure that we do not have to re-consent participants.

10.5 Objectives and End Points Summary

Primary Objective	**Primary Endpoint**	**Outcome Measures**
Efficacy of EC compared to NRT	Abstinence rates in each group at end of pregnancy	Prolonged abstinence at end of pregnancy from 2 weeks post-TQD defined as per Russell Standard abstinence criteria, biochemically validated
Secondary Objectives	**Secondary Endpoints**	**Outcome Measures**
Effects on Smoke and Nicotine intake from EC and NRT users; 'dual users'; and reducers (50% or more)	Change in smoke and nicotine intake from baseline to end of pregnancy	Salivary cotinine and anabasine
Efficacy of EC compared to NRT	Abstinence at 4 weeks post-TQD, end of pregnancy, and 3-months post-partum.	Self-reported point prevalence abstinence (not a puff over the previous week) at 4 weeks post-TQD, at end of pregnancy and at 3 months post-partum; self-reported prolonged abstinence at end of pregnancy and at 3-months post-partum
Treatment adherence	Use of EC and NRT	Self-reported EC and NRT use (number of days used; amount and products used; product changes)
Safety of EC compared to NRT	Adverse events throughout the intervention period and at 3 months post-partum (for both mother and infant). Birth and maternal outcomes	Self-reported adverse events and SAE's SAE's identified at 3-months post-partum follow-up calls. Birth and maternal outcomes: Birth weight; gestational age; C-section delivery; still birth/miscarriage/neonatal or post-neonatal death; maternal death; neonatal intensive care admission

10.6 Trial Design

A pragmatic multi-centre RCT comparing behavioural support and nicotine patch NRT (usual care) with the same behavioural support accompanied instead by EC.

Duration of participation: The length of duration in the study will vary depending on what stage in their pregnancy the participant is randomised into the trial. The maximum duration in the study will be 10 months (from earliest point of recruitment at 12 weeks gestation to the final follow up at 3 months post-partum, including an additional month to allow follow-up on non-responders). The minimum length of duration will be 7 months.

Number of visits: Participants will attend one session with the research team. Other study contact will be via phone apart from cases where the research team are able to collect the saliva sample in person.

10.7 Study Setting

Participants will be recruited by maternity services at sites across England, and by Stop Smoking Service in Scotland. We plan to include at least 23 recruiting sites across England and 1 site in Scotland, and have a further 6 sites in England, and 2 sites in Scotland as reserve sites, in case of slow recruitment rates. Queen Mary University of London is a non-recruiting, Non NHS Site, acting as the coordinating centre and performing intervention delivery, data collection and follow up telephone calls.

In England, Clinical Research Networks (CLRN) research midwives (RM) and routine care staff will recruit potential participants. In some sites RM may not be routinely available, but other relevant staff (such as clinical trial associates or research nurses) would be trained to carry out the research procedures. Those not eligible to take part in the study but interested in obtaining help with stopping smoking will be referred to local stop smoking services as per standard practice.

11.0 Eligibility Criteria

11.1 Inclusion Criteria

- Aged 18 years or over
- Daily smokers
- 12 to 24 weeks pregnant
- Wants help with stopping smoking
- Willing to be randomised to use either NRT or EC (to avoid selective drop-out and contamination)
- Wiling to receive 6 weekly support calls over the phone plus two follow-up calls
- Speaks and reads English to a level that permits data collection via the telephone

11.2 Exclusion Criteria

- Known allergic reaction to nicotine skin patches (a contraindication for patch use)
- Current daily use of NRT or EC
- Taking part in another interventional trial
- Serious medical problem or high-risk pregnancy at time of initial consent* (to avoid problems with follow-up and data collection)

* Note: we will not automatically withdraw participants from the study if their pregnancy becomes high-risk during the trial as this could bias the evaluation of safety outcomes.

12.0 Trial Procedures

12.1 Recruitment

Dependant on the Site setup, participants will be recruited by research midwives (RMs) or other appropriately trained staff (such as specialist pregnancy stop smoking service (SSS). The RM or SSS advisor would also take consent and conduct the baseline and randomisation visit and obtain birth and maternal outcomes data as required.

12.2 Participant identification

The usual care team will identify potential participants from patient records and send PIS and invitation letters alongside 12 or 20 week scan appointment letters; contact the participants via telephone, letter, email or text; or the research team may ask women to complete a screening questionnaire when they attend hospital for their ultrasound scan appointments. Community midwives who see pregnant smokers at booking appointments or at other routine care appointments will also be briefed to refer any pregnant smokers interested in the study to the research team. Posters advertising the study will also be placed within the sites' antenatal clinics, or in Scotland, at the participating SSS.

Potential participants identified by hospital records will be pre-screened to check that they meet some of the eligibility criteria, e.g. by checking they are 18 years of age, between 12-24 weeks pregnant and daily smokers. If offered the study by phone or in person, pre-screening will encompass all eligibility criteria.

Women identified as potential participants will receive the study information sheet (PIS) (depending on the recruitment route either in person or in the post/email) and an invitation to attend a screening and randomisation session or, where appropriate, a home visit. Participants will be given sufficient time to consider the PIS. A screening log will be kept by staff of how many people have been offered the study.

Confidentiality will be maintained at all times as all women in England and Scotland who are identified as smokers at their booking appointments are normally routinely offered stop-smoking support, either in-house or referred to a local stop-smoking service. No one outside of the direct care team will have access to identifiable personal information of any potential participants prior to consent. In some sites, the research team may be a part of the usual care team; where they are not, only the direct care team will access personal data and invite potential participants to the study.

12.3 Informed Consent Procedures

12.3.1 Responsibility for obtaining consent

The research team will be delegated by the local PI to obtain consent from participants. Local PI's will confirm eligibility and sign off consent forms after randomisation, but prior to dispensing of any study products. They will be blind to randomisation to avoid a possible bias. Staff taking consent will be trained in study consenting procedures and GCP (CTIMP) trained, this will be recorded in a Study training log within the ISF.

12.3.2 Consent Considerations

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where she may obtain further information about the trial. Where a participant is required to re-consent, for example if during the trial new Research Safety Information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a participant, it will be the responsibility of the CI and local PI to ensure this is done in a timely manner.

12.3.3 Population

Pregnant daily smokers (pregnancy gestation 12-24 weeks) who would like help to stop smoking and who are willing to be randomly assigned to receive either nicotine patches or an electronic cigarette (EC) as part of their treatment. They must also be willing to receive 6 weekly support calls over the phone plus two follow-up calls, one at the end of pregnancy and one 3 months post birth.

12.3.4 Vulnerable participant's considerations

N/A

12.3.5 Written/ reading / translation considerations

Participants must be able to speak and read English to allow data collection.

12.3.6 Participants lacking capacity

N/A

12.3.7 Minors

N/A

12.3.8 Consenting process

Participants will be provided with the Participant Information Sheet (PIS), and will be given sufficient time to consider the PIS and entry into the trial. When they see the research team, they will be asked to confirm they have read the PIS and will be invited to ask any questions they may have. Should the participant have any questions needing medical input or wish to speak to the PI, this will be arranged. If they are happy to be involved they will be asked to read through the consent form and to initial against each of the relevant statements to confirm their agreement. They will then be asked to print their name, sign and date, and the person taking consent will do the same. The original will be retained for the Investigator site file and a copy given to the participant for their own records and a copy for the pregnancy notes. The research team member will then update the consent log with the participant's details. The local PI will review and counter sign consent and confirm eligibility before the study product is dispensed.

12.4 Screening Procedures

Once consented, participants will be asked the eligibility questions to re-confirm their eligibility (see inclusion/exclusion criteria) in cases where pre-screening was either not done in full, or it was not done immediately before consenting. This is to check that nothing changed since pre-screening, to the day of consent.

Those not eligible to take part in the study but interested in obtaining help with stopping smoking will be referred to local stop smoking services as per standard practice. The research team will document these participants on the ineligible log.

12.4.1 Eligibility assessment

Once a participant has been randomised into the study, the local PI will be notified and asked to confirm their eligibility. They will confirm via their medical notes that the patient is between 12-24 weeks pregnant and is not deemed to be having a high-risk pregnancy. The local PI will then sign the consent form to confirm that consent has been taken as per protocol and to confirm eligibility; a copy will be placed in their medical notes. It will also be recorded on the e-CRF. If a patient is not eligible following the PI assessment, they will be notified and withdrawn from the trial. This will be recorded on the e-CRF and in their medical notes.

12.5 Patient Allocation

12.5.1 Randomisation Method

Consenting individuals will be randomized to one of the two treatment groups by an electronic database created by the Barts CTU. Randomisation will not be stratified by study site as we do not expect treatment outcomes to vary by site. Blocks of random sizes will be used. More details on the randomisation algorithm used will be provided in a study-specific SOP.

12.5.2 Randomisation Procedure

Consented and eligible participants will be randomised to a treatment arm at their baseline visit. A secure online database created by the Barts CTU will be used. This will incorporate an online case report form (CRF) that will generate a unique randomisation number. This number will be added to the randomisation log by the research team. The treatment allocation will be provided immediately by the program, which will also be added to the randomisation log.

A back-up randomisation procedure will be available during working hours (0900-1700) for occasions where access to the network or internet is unavailable. In this scenario, the research team will be able to email or fax completed CRF's to the CTU for a telephone randomisation. Details on this procedure will be provided in a study-specific SOP.

12.6 Blinding

N/A

12.7Unblinding

N/A

12.8 Trial Schedule

12.8.1 Schedule of Treatment for each visit

The following data will be collected and interventions delivered:

Baseline visit:
Demographic information, smoking history including whether participants live with other smokers, cigarettes smoked per day (cpd), nicotine dependence, previous stop smoking attempts and medication use, saliva sample to assess anabasine and cotinine levels to measure baseline smoke and nicotine intake, contact details of family and friends (to assist with follow ups where participants' contact details change).

Following randomization, a member of the research team will demonstrate how to use the allocated product. Further details on each intervention are described next. The research team will also arrange a suitable time for the first call from the stop-smoking advisor.

Once participants are randomised into the trial and the local PI confirms eligibility, the participants will be under the care of the local PI and staff at the trial co-ordinating centre, (HAL, QMUL).

Intervention details:

The initial and further supplies of patches or EC will be by mail, accompanied by behavioural support over the telephone.

Nicotine Patch: The study will use 15mg/16hr nicotine patch or 10mg/16hr for smokers who find the former too strong. They will be advised to wear one patch a day during waking hours as per its medicinal license. Medication will be posted form the QM main site. This is an open label RCT where the nicotine patches, a product available OTC, are being used within their medicinal licensing and so there are no special labelling or packaging requirements. The medication will be stored at the site in facilities that meet the requirements of GCP. The facilities for storage of the medication will be checked to ensure that the drug will remain stable and will be stored securely. The researcher will dispense the medication in accord with the protocol and will record the batch numbers on a log. Each person will be dispensed 2-week supply of patches initially and offered further supplies over the phone for up to 8 weeks. Patches will be sent via recorded delivery.

Electronic cigarette: The study will use a TPD-approved refillable EC (Innokin Endura T18; TPD product ID: 00132-16-00001) with a tobacco flavoured e-liquid with nicotine content of 18mg (fruit flavour e-liquid will be offered in cases where participants dislike the tobacco flavour). EC are a consumer product and this is an open label trial and so there are no special labelling or packaging requirements. Each person will be dispensed the starter kit with an initial supply of e-liquid and offered further supplies over the phone for up to 8 weeks. Supplies will be sent via recorded delivery.

Dose modifications: Participants who find their products too strong will be offered 10mg nicotine patches or 11mg e-liquid.

Weekly phone calls:
Participants will receive guidance on using their allocated product and support in preparation for the Target Quit Date (TQD), on the TQD, and weekly for four weeks thereafter (6 calls in total). The schedule and content of calls will follow the established protocols of pro-active telephone counselling for smokers (e.g. [44]).This support addresses issues such as planning for the quit day and how to deal with difficult situations, such as others smoking around the quitter. We will also collect smoking status and monitor use of EC and NRT and any other stop smoking medications, and adverse events. Study staff will also complete the study questionnaires with the participants.

End of pregnancy phone call (35 week gestation to ten weeks post-partum)
Smoking status; use of EC, NRT and any other stop smoking medications; adverse events. We will also collect birth and maternal outcomes with the prior consent of participants (date of birth, birthweight, gestational age, still births, miscarriage, maternal death, congenital abnormalities, neonatal and post-neonatal deaths, neonatal intensive care admission and delivery by C-section) from hospital records. Participants reporting abstinence from smoking, reduction of cigarette consumption of 50% or more, and those smoking and using NRT or EC, will be asked to provide saliva samples for cotinine and anabasine analysis. Sampling kits will be sent by post together with instructions, and self-addressed envelope for sample return. A visit will be offered if postal samples are not returned. Participants will be provide with £20 for their time in returning the saliva sample. The cut off points for classifying participants as abstainers will be cotinine < 15 ng/ml [42] for those not reporting using any nicotine product and anabasine< 1 ng/ml [43] for those reporting any NRT/EC use.

Three months post-partum phone call
Participants will be contacted to check on any adverse events to themselves or their infant since end of pregnancy, and to record smoking status and product use.

12.8.2 Schedule of Assessment (in Diagramatic Format)

	Study session									
Measures/ Procedures	**Baseline**	**Pre TQD**	**TQD**	**TQD+1 week**	**TQD+2 weeks**	**TQD+3 weeks**	**TQD+4 weeks**	**TQD+6 weeks**	**Birth FU**	**3 month post birth FU**
Informed consent + screening	X									
Baseline questionnaire	X									
Randomisation	X									
Saliva sample	X								X	
Smoking status/CPD	X			X	X	X	X		X	X
Adverse events				X	X	X	X		X	X
EC/NRT use				X	X	X	X		X	X
EC/NRT demonstration	X									
Birth + maternal outcomes									X	
Behavioural support		X	X	X	X	X	X			
Supply of EC/patches		X			X		X	X		

12.8.3 Trial assessments

N/A- please see schedule of assessments

12.8.4 Follow up Procedures

Participants will be contacted for 2 data collection follow up calls post intervention; one at the end of pregnancy (35 week gestation to ten weeks post-partum) and the other 3 months post-partum. Participants will be sent a text message a few days before the call is due to ask for a suitable time to call. The QM team will attempt telephone contact first. If this is unsuccessful, participants will also be contacted via text, email and letter. There may also be the opportunity for the research team at the local site to see the participant at the clinic or to arrange a home visit. If the participant is agreeable to this, the research team will collect the follow up questions and return the saliva sample.

At three months post-partum, the study team will make 3 telephone attempts to contact the participant to collect further safety and outcome data.

Preventing distress: Many women who miscarry can participate in follow up without upset; however, calls can occasionally be distressing (e.g. relatives answering after maternal death). We will not routinely exclude women who have miscarried from follow up, but the following will minimise potential distress. The co-ordinating trial office will send the local research teams a list of participants to be followed up within the next fortnight; the local research team will be asked to identify anyone they either know to have or whose medical records show them to have experienced an event which might make follow up distressing. The opinions of the local research team will be considered when deciding whether or not to attempt follow up. In addition to this, a text reminder will be sent to all participants the day before their follow up call is due. Participants may then text back if they do not wish to be called. A reminder text will also allow participants to schedule a convenient time for their call. Participants will be able to text back their smoking status if a call is not convenient.

12.9 Withdrawal criteria

Participants will be able to withdraw from the study at any time. This will not put at risk their usual medical care. Failure to be contacted as part of the study will not count as withdrawal from the trial; the only study withdrawals will be those where participants have asked to be withdrawn from all further study procedures (i.e. withdrawal of

consent). Such participants will not be replaced and data collected up to the point of their withdrawal will be used in the study analysis. At withdrawal, we would also seek permission to still use medical records data to assess safety.

Participants will be free to stop using the allocated treatment at any time. This is one of the study outcomes and will not trigger any withdrawal procedures. However, in the event of a SUSAR or SAE that is judged to be related to NRT or EC, the CI will review the case and if deemed appropriate, the participant will be advised to stop using the medication.

12.10 Early withdrawal

Participants that withdraw their consent would not be followed up at the end of pregnancy and at 3-month post-partum. Those who withdraw from treatment but agree to further follow-up, would be contacted for any remaining weekly data collection and follow-ups. Please see section Laboratories and Samples with regards to the use of saliva samples from withdrawn participants.

12.11 End of trial (EOT)

The study would be completed and the REC informed, 6 months after the final participant has been followed up for their 3m post-partum follow-up, to allow for saliva sample analysis to be completed.

13.0 Laboratories and samples

13.1 Central Laboratories

ABS laboratories will be used for cotinine and anabasine analysis. ABS 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 ABS laboratories is as follows:

Dr Mira V. Doig
ABS Laboratories Ltd.
Biopark, Broadwater Road
Welwyn Garden City
Herts AL7 3AX

Main tel: +44(0)1707 358666
Direct line: +44(0)1707 358669
Mobile: +44(0)7776 212863
Fax: +44(0)1707358667

The Health and Lifestyle Research Unit (HAL) at QMUL, will also serve as a central laboratory, as saliva samples will be stored here for up to 3 years prior to analyses.

The contact details are as follows:

Dr Dunja Przulj and Dr Katie Myers-Smith
HAL, QMUL
2 Stayner's Road

London
E1 4AH

Tel: 0207 882 8230
Email: health-research@qmul.ac.uk

13.2 Local Laboratories

N/A

13.3 Sample Collection/Labelling/Logging

Saliva sample to assess anabasine and cotinine levels (including 3OH cotinine) will be collected by the research team at the first visit; and mailed by participants themselves or collected by the research team at the end of pregnancy. For the end-of-pregnancy sample collection, sampling kits will be sent directly to participants along with instructions on use and a self-addressed envelope. Participant will receive a text to inform them when the sample kit has been sent and a phone call to confirm receipt and guide them through sample collection if needed.

Participants will be asked to insert the saliva swab into their mouth and leave in the mouth for approximately two minutes or until saturated, and to then insert the swab into the small inner chamber of the swab storage tube and replace the cap securely.

Samples will be labelled with a participant ID number, the time point in which the sample is being collected (e.g 'baseline') and a date of when the sample was collected. The sample will be logged by the research team and sent via recorded delivery to the HAL laboratory for storage. The sample will not need to be temperature-controlled during its transfer to the HAL laboratory, as the sample is stable for up to 2 weeks before it requires freezing.

Samples collected by the research team will aim to be mailed within 24 hours, and no later than 2 weeks. Participants will be also asked to mail the samples within 24 hours of collection. Upon receipt, the samples will be logged by the QM team and stored in at -20°C in a designated freezer for biological samples. The freezer will be kept in a closed room and the temperature will be monitored. Samples will be stored for up to three years and will be send to ABS Labs together as described below.

If a participant withdraws their consent and explicitly states that they do not wish for their data collected thus far to be used, the sample will be destroyed.

13.4 Sample Receipt/Chain of Custody/Accountability

Samples will be packaged and delivered from HAL, 2 Styaner's road, London E1 4AH to the ABS laboratory by a contracted courier insured to handle medical samples (a trial-specific SOP will be followed). The saliva samples being sent will be documented on a log to be cross-checked by ABS laboratories once the samples are received. ABS laboratories will sign for receipt of the saliva samples and confirm receipt with study site. Samples will be kept frozen until analysis.

13.5 Sample Analysis Procedures

13.5.1 The arrangements for sample analysis

Samples will be analysed at the end of the study by ABS Labs (sections above and below describe how the samples will be handled prior to this). Cotinine and anabasine in human saliva samples will be determined using high performance liquid chromatography coupled to tandem mass spectrometry with multiple reaction monitoring (LC-MS/MS) after basification of the saliva and then liquid -liquid extraction with dichloromethane using cotinine d_3 and

anabasine d_4 as the internal standards. The analysis will be performed over 1 to 600ng/mL for cotinine and 0.1 to 10 ng/mL calibration range for anabasine.

13.5.2 Sample Storage Procedures

Prior to analysis, samples will be stored frozen in ABS Laboratories as per standard operating procedures If a participant withdraws their consent and explicitly states that they do not wish for their data collected thus far to be used, the sample will be destroyed by ABS Laboratories Ltd. without analysing it.

13.6 Sample and Data Recording/Reporting

Data will be pseudo anonymised and only contain a participant ID number. Data will be reported as per the analysis plan.

13.7 Processes at the end of study

All samples will be analysed prior to the End of study notification. Once analysed and the data has been received and reviewed, the samples will be destroyed by ABS Laboratories Ltd

14.0 Trial Medication

14.1 Name and description of investigational medicinal product(s)

Nicorette Invisi (also known as NicAssist Translucent) 10mg and 15mg/16 hours Transdermal Patch.

Description: Semi-transparent, beige, imprinted 13.5 cm2 (15mg) or 9 cm2 (10mg) rectangular TTS with rounded corners. Centrally located on a rectangular, aluminized and siliconized release liner.

Note: The e-cigarette (EC) is not as an IMP in this study as it is a consumer product regulated under the Tobacco Products Directive. We will be providing an EC starter pack to participants (see intervention details), but they will be encouraged to purchase a different EC and/or e-liquid if the one provided does not work for them. This is the current approach by stop-smoking services (e.g. Leicestershire, Bristol and the City of London SSS) who provide EC starter packs as part of standard care and encourage clients to switch to other EC products if needed.

14.2 Legal status of the drug

Nicorette Invisi patches are a licensed product in the UK, and licensed for use in pregnancy with the following indication;

Nicorette Invisi Patch relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.

15mg - PL 15513/0160
10mg - PL 15513/0160

14.3 Summary of Product Characteristics (SmPC)

Please see Nicorette Invisi 15mg patch/NicAssist Translucent 15mg Patch for a summary of Product Characteristics that will be used for the trial (version: 25 May 2016). If an update to this version occurs during the trial, the amendments will be reviewed and if of significance to the safety or integrity of the trial, action will be taken to amend the protocol and study procedures as required.

14.4 Drug storage and supply

IMP will be stored securely at the Health and Lifestyle Research Unit (HAL), 2 Stayner's Road, London E1 4AH. The IMP is to be stored below 25 degree Celsius in line with the manufactures guidance. A week-day temperature log will be kept.

The IMP will be supplied once participants have been randomised. This will be dispatched via Royal Mail recorded delivery, as is standard in some SSS who provide NRT on direct supply (as opposed to prescription). The IMP will not be temperature-regulated during transportation as this is not standard protocol in the SSS.

14.5 Supplier

N/A

14.6 Manufacturer

McNeil Products Ltd. Foundation Park, Roxborough Way, Maidenhead, Berks, SL6 3UG.

14.7 How the drug should be stored

The IMP will be stored as per manufacturer requirements. The SmPC states that the drug should not be stored above 25 degrees Celsius, and should be stored out of reach and sight of children and animals.

14.8 Details of accountability

Receipt: Upon receipt of the medication at HAL, a member of the study team will sign for the delivery and check contents. If there are any discrepancies, the study team will alert the suppliers. This will be recorded on the accountability log. The temperature in the storage area will be logged on arrival.

Supply: When a pack of medication is to be dispensed to a participant, the date of posting and the participant ID number will be recorded on a log along with the quantity and strength of medication dispensed.

Receipt by participant: Once the participant has received the medication, confirmation and date of receipt will be recorded on the log.

14.9 Medication destruction/return and Recall

There is no requirement for participants to return used packaging or unused IMP any destruction will be undertaken as per the manufactures instruction.

The study team will sign up to recall alerts via the MHRA. In the event of a recall, the research team will review the accountability logs for stock held at the HAL and IMP supplied, and any affected stock will be quarantined and the sponsor informed. If subjects have supply of the affected products they will be contacted to cease use of the IMP.

14.10 Prescription of IMP / Placebo/NIMP

N/A

14.11 Preparation and labelling of IMP

The nicotine patch will be used on-label and as per the packaging instructions, no trial-specific labelling or preparation of the IMP is required.

14.12 Preparation and Administration of IMP

No trial-specific preparation is required.

Participants will self-administer the product with telephone support from the study team: Participants will be advised over the phone that from their TQD the patch is put on as soon as they wake and removed before going to sleep. The following day a new patch will be placed in an area different to the day before to minimise adverse skin reaction. Participants will be advised to place anywhere they feel comfortable and also secure i.e. upper arms, thighs, back.

14.13 Dosage schedules

Participants will be asked to use one patch per day for up to 8 weeks, as is usual in the stop-smoking services. Participants will be asked to report on their patch use at each follow up call.

14.14 Dosage modifications

If participants report that they feel the patch is too strong, i.e. they experience discomfort or nausea, they will receive a lower strength patch (see dosing schedule below).

Dosing Schedule:

Starting strength:	15mg (one patch per day)
Reduced strength:	10mg (one patch per day)

14.15 Known drug reactions and interaction with other therapies

Nicorette Invisi Patch may cause adverse reactions similar to those associated with nicotine given by other means, including smoking, and these are mainly dose-dependent. At recommended doses Nicorette Invisi Patch has not been found to cause any serious adverse effects. Excessive use of Nicorette Invisi Patch by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

14.16 Prior and Concomitant medication

No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established.

14.17 Trial restrictions

N/A

14.18 Assessment of compliance

Compliance will be assessed by asking participants each week on how many days they used their nicotine patch. Treatment adherence is a secondary outcome of the trial, and as such non-compliance will not lead to participants being withdrawn from the study or any follow-up procedures.

14.19 Arrangements for post-trial access to IMP and care

Participants will receive 8 weeks supply of patches. Should they require further treatment, they will be referred to their local stop-smoking service or GP.

15 Pharmacovigilance

15.1 General Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: See 17.6 for events related to underlying pregnancy that will not be reported
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

15.2 Site Investigators Assessment

Once participants are randomised into the trial and the local PI confirms eligibility, the participants will be under the care of staff at the trial co-ordinating centre (HAL, QMUL). The local PI at HAL will be responsible for their care (or in his/her absence an authorised medic within the research team) and assessment of any event for:

- Seriousness
  Assessing whether the event is serious according to the definitions given in section 15.1.

- Causality
  Assessing the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

- Expectedness
  Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

- Severity
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

15.3Reference Safety information

The SmPC for the Nicorette Invisi 15mg Patch (section 4.8, version: 25 May 2016) will be used for assessing whether an adverse reaction is expected.

15.4 Recording of Adverse Events or Reactions

The following are considered expected AEs/ARs:
Symptoms which are potentially caused by NRT/EC use and are listed as known events/reactions in the SmPC for patch, which include: rash/local skin irritation; nausea/vomiting; headaches; dizziness. Known reactions to EC include dislike of taste, cough and throat/mouth irritation.

All AEs and ARs will be recorded in the e-CRF and the participant followed up by the research team to resolution as appropriate. AE's will begin to be recorded from receipt of the study product by the participant until the end of the follow-up period.

15.5 Notification of AEs of special interest

There are no AESIs identified for this study.

15.6 Serious Adverse Events that do not require expedited reporting

The following will be considered **expected serious adverse events (SAEs) and will not be reported in an expedited manner** (see section 15.7) but will be recorded.

Events requiring hospital admission (overnight stay) which are related to the underlying pregnancy, these include: recognised pregnancy or postnatal complications, including pre-term delivery, low birth weight, birth injury, infection, thrombosis, haemorrhage, hypertensive disease, instrumental delivery, caesarean section, and antenatal admissions for pregnancy related diseases such as false labour, infection, thrombosis, haemorrhage, hypertensive disease, suspected or confirmed foetal compromise, vaginal bleeding foetal congenital abnormalities, and infant hospital admissions; and incidental hospital admissions for minor, gastrointestinal diseases, respiratory, cardiac, renal skin, psychiatric and neurological problems.

15.7 Notification and Reporting of Serious Adverse Events & SUSARs

The following **will be considered Serious Adverse Events (SAEs) which will require reporting**: Baby: foetal death, still birth, neonatal and post-neonatal death; Maternal: maternal death. Other events requiring hospital admission (overnight stay) apart from those related to the underlying pregnancy or a pregnancy related condition. SAEs will begin to be recorded from receipt of the study product by the participant. Unresolved SAEs will be followed up until the end of the study at three months post-partum if the participant is still using the study product.

All Serious Adverse Event (SAEs) will be reported to Barts CTU, acting on behalf of the sponsor, within 24 hours of the PI or research team becoming aware of the event. SARs must also be reported to Barts CTU, acting on behalf of the sponsor, within 24 hours of the PI or research team becoming aware of the event. The Barts CTU will email the de-personalized SAE to the sponsor within 1 working day of receipt.

Day zero for reporting to the MHRA is the day that the Barts CTU is notified of a medically assessed SUSAR. SAEs should also be recorded in the patient notes and the e-CRF.

The initial report must be made by completing an SAE e-CRF accessible via the web application. In addition the SAE e-CRF 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 should be completed and faxed or emailed. 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 blacked out and information not visible.

15.8 Sponsor Medical Assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of SAEs and SUSARs to the CI. The CI (or CI's delegate in his absence) must review all SAEs within 24 hours of receipt. This review should encompass the event, narrative, outcome, seriousness, relatedness and expectedness.

The CI will be assisted in identifying trends and maintaining oversight of IMP safety profile through trial committees as per section 27.0.

15.9 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken

immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed changed with the Sponsor and Medical Advisor at the MHRA (via telephone) prior to implementing the change if possible.

The CI has an obligation to inform both the MHRA and Research Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The sponsor (QMUL) must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

15.10 Procedures for reporting blinded SUSARs

N/A

15.11 Pregnancy

All participants will be pregnant during the trial. The DMEC comprises of an independent neonatologist, who will be able to provide oversight on safety issues pertaining to pregnancy.

16.0 Annual reporting

16.1 Development Annual Safety Update (DSUR)

The DSUR will be written by the CI (using Sponsor template) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "notice of acceptance letter" from the MHRA. As delegated Sponsor Medical Assessor the CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. REC will be sent a copy of the DSUR.

16.2 Annual Progress Report (APR)

The APR will be written by the CI (using HRA template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

17.0 Statistical and Data Analysis

17.1 Sample size calculation

Risk ratios (RR) of abstinence for nicotine replacement treatments is on average 1.6, with RR 1.9 for nicotine inhaler and 2.02 for the faster acting nasal spray [27]. EC provide nicotine with a speed comparable to the nasal spray, but are much easier to use. Data from UK services suggest that the efficacy of EC is better than that of other treatments [25, 26] but this is not from randomised trials and so needs to be interpreted with caution. It is, however, comparing EC effects with those of other treatments that are effective. In contrast to this, NRT in pregnancy had the same efficacy as placebo [14].

Extrapolating from the results of previous UK pregnancy trials, we estimate the quit rate at delivery in the control arm of 8% [14]. Based on the above considerations, we estimate that EC will at least double this very low outcome, but for the purposes of power calculation, we estimate the quit rate in the EC arm conservatively at 14% (odds ratio 1.87). For 90% power, 1,140 participants will be needed altogether (570 in each condition; alpha=0.05, two-tailed test) to detect this difference. This sample size would allow us to detect smaller treatment effects with lower power,

e.g. we would have 80% power to detect a difference between 8% and 13.1% (odds ratio 1.74). We will provide an estimate of the difference with a 95% confidence interval to show the range of possible sizes of any effect.

17.2 Planned recruitment rate

We will aim to recruit on average 3 participants per month from each of the planned sites. Recruitment rates will be monitored monthly and additional sites will be recruited if needed. A 6 month recruitment pilot phase is included in the trial, as per the funder's request. The table below presents an assessment of how overall recruitment within the first 6 months of the trial recruitment period should be assessed by the Trial Steering Committee (TSC), in conjunction with the co-ordinating trial centre.

Number recruited in 6 M	**Interpretation of recruitment rate**	**Required actions**
≥ 288	Maintaining this rate will achieve trial target sample size	Continue trial with regular TSC meetings, no further formal review of recruitment required
201-288	Improvements needed to achieve trial target sample size	Present action plan to TSC with clear and achievable strategies for overcoming identified recruitment barriers and/or recruit extra trial centres. TSC to manage this plan without referring to HTA. TSC to formally assess recruitment again in 6 months (12 months into trial).
160-200	Substantial improvement is needed to achieve trial target sample size	As above – action plan commensurate with recruitment difficulties; HTA will be notified; if TSC judge the plan adequate, trial may continue. If not satisfied with plan, TSC will ask HTA opinion. Formal TSC recruitment review in 6 months (12 months into trial).
<160	Risk of failing to achieve target sample size without improvement	Rescue plan will be considered by TSC and HTA commissioning board; monitoring visit from HTA; joint decision on whether trial should continue

17.3 Statistical analysis plan (SAP)

A detailed description of analysis will be provided in the statistical analysis plan to be agreed with the trial steering committee and the DMEC and finalised prior to completion of data collection.

We will present baseline characteristics according to treatment group for the main baseline covariates, and compare baseline characteristics between those who do and do not provide primary outcome data to examine the pattern of missingness in the data.

Analysis will be performed on an intention to treat basis, with participants who, for any reason, have missing outcome data presumed to be smoking.

17.4 Summary of baseline data and flow of patients

See Trial Schedule (section 12.8) and Trial Flowchart (section 9).

17.5 Primary outcome analysis

The primary outcome will be prolonged abstinence reported throughout pregnancy as per Russell Standard (RS) criterion of abstinence [42] (smoking no more the five cigarettes from 2 weeks post-TQD, with no smoking at all over the previous week at end of pregnancy) and validated biochemically at end of pregnancy by salivary cotinine levels of <15 or salivary anabasine levels of <1 ng/ml in participants using nicotine containing products at the time. Participants lost to follow-up or anyone with missing smoking status data for any reason at follow-up, will be classified as smokers. We will compare e-cigarette and NRT treatment groups, using logistic regression. We will conduct sensitivity analysis using the Hedeker method to explore alternative assumptions about the missing data. Full detail on analysis will be provided in the Statistical Analysis Plan.

17.6 Secondary outcome analysis

Secondary and safety outcomes will also be analysed on an intention to treat basis where possible. Binary outcomes including self-reported quit rates at 4 weeks post-quit and at end of pregnancy, and 7-day point-prevalence abstinence will be analysed by logistic regression and continuous outcomes, including birthweight and gestational age by multiple linear regression. In infant outcomes analysis we will allow for clustering in multiple births.

17.7 Subgroup analyses

N/A

17.8 Interim analysis and criteria for the premature termination of the trial

N/A

17.9 Study Subjects

All participants randomised into the study will constitute the population whose data will be analysed. Analyses will be intention-to-treat, and participants will be retained in the groups to which they were originally allocated to.

17.10 Procedure(s) to account for missing or spurious data

In smoking cessation trials, missing data is not random – smokers who fail in their quit attempt typically avoid follow-up contact while those who succeed are keen to attend. Participants lost to follow-up will be included as smokers.

18.0 Data Handling &Record Keeping

18.1 Confidentiality

The Chief Investigator has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined in the JRMO SOP 20 Archiving.

The Chief Investigator and the study team will adhere to these parameters to ensure that the Participant's identity is protected at every stage of their participation within the study. At time of consent each participant will be allocated a unique participant number (by the on-line database system) before undergoing any screening procedures. When

randomized into the study, each participant will have a unique randomization number provided by the online database system.

Identifiable data will also be collected and stored in an encrypted database or password protected file with restricted access to authorised staff on a secure server. Identifiable data will be stored separately from the clinical data. This is required to allow weekly phone calls and follow-up data collection. This will include name, address, email, telephone number, GP details, NHS number and date of birth. The patient's GP will be informed of the patient's participation in the study if they consent to it. Only study personnel and the study sponsor will have access to study data.

All information will be kept confidential. Copies of all documents regarding the study will be kept in the trial master file (TMF) and/or relevant site file.

18.2 Data Custodian Details

The grant holder, Peter Hajek, is the custodian of the research data.

18.3 Psuedononymisation

Once consented into the study, participants will be given an ID number made up of their initials and day of birth. This information will be kept on a log. Once the participant is randomized into the study, they will be assigned a unique randomization ID number, generated by the database. This information will be kept on a log.

18.4 Transferring/Transporting Data

N/A

18.5 Data collection tools and source document identification

All data will be entered onto the e-CRF system. Paper CRF's will be available in cases where the online e-CRF system is offline. Once online again, the data will be entered and the paper CRFs filed away.

18.6 Source Data

Source documents will comprise of birth and maternal outcomes from hospital records; this data will however be entered onto the e-CRF system as per all other data collection, and as such will remain anonymous.

18.7 Case Report Form

Elements of the e-CRF database will include:

- Registration
- Eligibility screening
- Dates
- Randomisation and product allocation
- Baseline and weekly questionnaires
- Follow-up questionnaires
- AE and SAE forms
- Withdrawal from study
- Study product dispensing
- Confirmation of sample collection

The local research team will be responsible for completing the baseline, screening and randomization elements of the CRF, and sections pertaining to follow-up (e.g. smoking status, birth and maternal outcomes). The trial coordinating centres will deliver the weekly phone calls and conduct data collection, follow-up, and complete withdrawal and SAE forms.

18.8 CRFs as Source Documents

Data will be recorded directly to a database using online Electronic Case Report Forms (eCRFs). The eCRFs will be managed by a secure web application, accessible via HTTPS/SSL. Users will be issued with a username and password and will be required to login for web application access; their activity will be tracked using unique user identities and their access to data controlled by defined access roles.

A paper backup system will be established in case of technical failure. Where paper CRFs are used, they will be entered onto the database as soon as it is available, and the paper copy will be filed away.

The eCRFs will be completed by suitably trained research staff, as designated in the site delegation log, as accurately and completely as possible throughout the study.

18.9 Data handling and record keeping

Data will be recorded directly to a database using online eCRFs (see details above). Validation rules will be applied to ensure the validity and quality of the data. The database will have an audit trail. All study staff will be trained on how to use the database, and this will be logged on a training log. Identifiable data will be collected and stored in an encrypted database or password protected file with restricted access to authorised staff on a secure server. Identifiable data will be stored separately from the clinical data

All copies of original signed consent forms will be filed in the TMF.

18.10 Access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Only study staff (e.g. those collecting data, the CI, study managers, CTU staff etc) will have access to the data.

19.0 Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Sponsor Policy that the records are kept for a further 20 years.

All paper information relevant to the study will be archived and retained for 20 years at the Barts Health NHS Trust facility in Prescot Street. Electronic CRF data (which will not include personal identifiable data) will be kept on a secure online database for 20 years, following the Barts CTU's SOP on electronic archiving.

Destruction of essential documents will require authorisation from the Sponsor.

20.0 Monitoring, Audit and Inspection

20.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the Sponsor and Chief investigator based on the sponsor's trial risk assessment; this will include on site monitoring at least once a year

20.2 Audits and Inspections

The Sponsor (or delegate), Barts CTU and funders, retain the right to Audit any aspect of this trial, trial site or central facility. In addition, any part of the trial may be inspected by the regulatory bodies where applicable.

20.3 Notification of Serious Breaches to GCP and/or the protocol

A serious breach is defined as a breach that is likely to affect to a significant degree: the safety or physical or mental integrity of the participants; or the scientific value of the trial.

The Site Principal investigator is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours.**

The Chief Investigator is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours**.

The sponsor will work with the CI to investigate any potential breach and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach.

20.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current Research Governance Framework, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

20.5 Non-Compliance

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The CI will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated.

CI and the coordinating team should assess the non-compliances and action a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the sponsor within 24 hours of the Coordinating team becoming aware.

Where applicable corrective and preventative actions CAPA should be assigned. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, including an on-site audit.

20.6 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enrol participants into the trial, the Principal Investigator or designee will apply for NHS Site confirmation of capability and Capacity as per HRA guidelines.

For any amendment that will potentially affect a site's confirmation of capability and capacity, the Principal Investigator or designee will follow local procedures to confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

Before the start of the trial, approval will be sought from the Research Ethics Committee (REC) and MHRA for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Decision whether an amendment constitutes a minor or substantial amendment lies with the sponsor.

Substantial amendments that require review by the Sponsor and REC and MHRA (where relevant) will not be implemented until the REC and or MHRA grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the Sponsor, REC and MHRA will be retained in the Trial Master File at the lead site and Investigator Site File at each site.

The Chief Investigator will notify the REC, MHRA and Sponsor of the end of the study.

21.0 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator, Robert Walton has provided consultancy to manufacturers of stop smoking medications.
The Trial grant holder, Peter Hajek has received research funding from and provided consultancy to manufacturers of stop-smoking medications.

A declaration of Conflict of interest from local PIs and committee members will be sought, and filed in the TMF.

22.0 Ethical and Regulatory Considerations

Please section 8.2 of the introduction for a discussion on the safety and risks of e-cigarettes used in pregnancy.

23.0 Peer review

The study has undergone an institutional peer review by Prof Malcolm Law, Professor of Epidemiology and Preventive Medicine, Wolfson Institute of Preventive Medicine, Queen Mary University; and an independent peer review by 6 independent reviewers as part of the NIHR HTA (funders) grant application process.

24.0 Public and Participant Involvement

The trial proposal is based on extensive patient and public involvement. EC were discussed on two occasions with our panel of smokers and the panel thought it was urgent to examine how EC efficacy compares with standard treatment. This influenced the decision to propose an effectiveness trial. Four pregnant smokers seen by our pregnancy advisor have also been consulted. All had heard about EC and one tried a cig-a-like product but did not like it. All thought it important to establish whether EC can help pregnant smokers quit. A member of the New Nicotine Alliance, a forum for EC users (a charity that does not receive tobacco or e-cigarette industry funding) was consulted on the development of this trial; she smoked through two pregnancies before stopping smoking using e-cigarettes.

At our Annual 'Update and Supervision Day' for advisors working within Stop Smoking Services, advisors working with pregnant women reported an increased use of EC in this group and reported their own uncertainty on whether to discourage, condone, or encourage such use. Participants thought that a trial clarifying the efficacy and safety of EC in pregnancy would have important practical impact nationwide. This was the initial impetus for developing the present proposal.

In January 2017, we convened a panel to test three EC. All four members of the panel were current smokers. One was a current EC user and had used EC during her pregnancy; two were previous EC users, and one had never tried EC before.

The three different EC tested were the Innokin T18 (also branded as the One Kit by the UK E-cig Store), The Arc Mini by TECC, and the Arc 3 by TECC. We chose only to test tank-based EC as evidence suggest they are more effective in delivering nicotine than the 1st generation cig-a-like ECs. We were also advised by stop-smoking pregnancy advisors at our Annual Update and Training Day (Dec 2016), that most women they were seeing were using tank-based EC.

Two of the panel recommended the Arc Mini and two recommended the Innokin. The Arc 3 was described as 'too large and bulky' and one of the panel thought it would not be discreet as it created the most amount of vapour and was the largest device. Two of the panel recommended the Innokin on the basis that it would be discreet, was easy to hold and more handy, and there were no confusing digital displays. The other two recommended the Arc Mini on the basis that it was a good size and discreet; and gave good enough vapour.

Based on this feedback, we opted to use the Innokin device over the Arc mini due to its ease of use (e.g. it is not variable voltage, there is no digital display). We also have extensive experience with this device as it is currently being used in another large NIHR funded EC trial.

25.0 Indemnity

Insurance and indemnity will be provided by Queen Mary University of London.

26.0 Access to the final trial dataset

Only the investigators and other key study staff (e.g. CI, Grant holder CTU staff, and study manager) will have access to the final trial dataset.

27.0 Trial Committees

A **Trial Management Group** (TMG) comprising selected co-investigators, and key employed staff will meet monthly to check on the practical details of the trial and progress. The mix of co-investigators who attend will vary between meetings, depending on the stage of the trial and the priorities at different stages of the project. The CI will attend all meetings.

External oversight will be provided by a **Trial Steering Committee** (TSC), which will include key members of the study team; an independent Chair, and three other independent members with smoking cessation and perinatal trials experience; and.at least one lay PPI member.

A **Data Monitoring (and Ethics) Committee** (DMEC) will be convened to review safety data and will meet every 6-12 months. Members of the DMEC will include an independent Chair, and independent neonatologist and an independent statistician. SUSARs will be reported to the DMEC chair along with the treatment allocation group of the trial subject and a cumulative count of SAE and SUSAR frequency in each trial arm. SAEs which are not considered SUSARs will be reported in an unblinded manner to each DMEC meeting.

28.0 Publication and Dissemination Policy

28.1 Publication

The findings of the trial will be published in a peer-reviewed journal at the end of the study. They will also be published on EUDRACT within one year of the end of the trial, and on the ISRCTN, where the trial has been registered.

28.2 Dissemination policy

We will use existing relationships with guideline producers internationally, so that findings are incorporated into guidance. Our team also collaborates with the National Centre for Smoking Cessation Training (NCSCT) and will work with this organisation to modify online training modules used by all NHS smoking cessation professionals, as appropriate. We will ensure that findings are highlighted to the Department of Health, devolved governments and health charities, as appropriate. We are particularly well-equipped for this through membership of the UK Centre for Tobacco and Alcohol Studies (UKCTAS). UKCTAS has strong links with key national and international policy and practice organisations.

If participants request the results they will be provided with a summary of the findings.

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