JRMO Research Protocol for Interventional Studies

Full Title Do e-cigarettes help smokers quit when not accompanied by intensive behavioural support?

Short Title	**Vapeline**
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List of laboratories	NA
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List of central facilities	NA

1. Contents

2. Glossary

AE- Adverse Event
AR- Adverse Reaction
CI- Chief Investigator
CPD- Cigarettes Per Day
CRN- Clinical Research Network
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
RN- Research Nurse
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

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Dr Katie Myers Smith**

Signature: 

Date: **04.08.2020**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: **Dr Francesca Pesola**

Signature:

Date: **04/08/2020**

4. Summary and synopsis

Short title	Vapeline
Methodology	Randomised controlled trial (RCT)
Research sites	Queen Mary University of London (non-NHS) University of Edinburgh (non-NHS) Bradford Teaching Hospitals NHS Foundation Trust (secondary care) Gateshead Health NHS Foundation Trust (secondary care) Barts Health NHS Trust (secondary care) Homerton University Hospitals NHS Trust (secondary care) NIHR CRN: North Thames (primary care) NIHR CRN: North East and North Cumbria (primary care)
Objectives / aims	***Primary:*** To determine the 6-month sustained biochemically validated abstinence rates in smokers using EC with telephone support vs those using EC without support; and those using EC without support vs smokers using free online support (standard care). ***Secondary:*** To determine the 12 month sustained biochemically validated abstinence rates, the sustained biochemically validated abstinence rates between 6 and 12 months, effects of the intervention on self reported 7-day point prevalence abstinence at 4 weeks, 6 and 12 months, change in cigarette consumption at all three follow-up points, frequency and severity of urges to smoke and change in constipation and mouth ulcers at 4 weeks, self-reported weight change and respiratory symptoms at all three follow-up points, treatment ratings and adherence including EC use at each time point, adverse reactions, cost effectiveness of interventions, primary and secondary care health care professionals' (HCPs) and smokers' views of an EC helpline (vapeline).
Number of participants	1170
Inclusion and exclusion criteria	The main trial will recruit adult daily smokers (18 years or over) who are motivated to stop smoking, own a mobile phone, and who are willing to try either an online and/or texting treatment package, or EC with or without telephone

	support and receive follow-up calls and are able to read/write/understand English. Exclusion criteria include pregnancy and current use of EC (at least weekly). The qualitative sub study will recruit health care professionals who treat smokers, participants already taking part in the main study, and smokers not taking part in the main study. The only other inclusion criteria is being able to read/write/understand English. There are no exclusion criteria.
Statistical methodology and analysis (if applicable)	Validated abstinence rates will be compared between the study arms using general linear models. Participants lost to follow-up or not providing biochemical validation will be included as non-abstainers as per Russell Standard.
Study duration	The total duration of the project is 45 months. Six months to set up the study and obtain regulatory approvals. Twenty-one months to enrol 1,170 participants; 12 months to complete follow-ups, 6 months to analyse the data and write up the results. The study start date is 1/9/2020. Recruitment is due to start on 1/3/2021. The estimated date of last follow up is 30/11/2023 and planned end date of the whole trial is 31/5/2024.

5. Background

Electronic cigarettes (EC) are devices that in addition to nicotine provide sensory input similar to that provided by conventional cigarettes. EC deliver nicotine at least as efficiently as licensed nicotine replacement treatments (NRT) (1, 2) and provide better relief of urges to smoke acutely (3-6) as well as throughout the initial period of abstinence from smoking (7). EC are also less expensive than smoking cessation medications and are more attractive to smokers (8, 9).

Using EC (vaping) for up to two years was not found to generate any adverse health effects so far (10). Based on the comparisons of chemicals generated by cigarettes and EC, it has been estimated that the risks of long-term vaping are unlikely to exceed some 5% of health risks of smoking (11). The current UK position is that if smokers switch to vaping, this will reduce the toll of smoking-related death and disease and benefit public health (11-13). The UK has some of the most comprehensive regulations of EC in the world, with manufacturers required to comply with a mandatory notification scheme, child and tamper proof packaging with health warnings, and limits on nicotine content (14).

Two early randomised controlled trials (RCTs) showed that nicotine containing EC are more effective in helping smokers quit than placebo EC (15, 16). One of these trials also compared an early model of low nicotine delivery EC and nicotine patches. Participants were provided with minimal or no behavioural support. Both interventions were associated with similar low 6-month sustained validated abstinence rates from smoking (7.3% vs. 5.8%). EC generated better smoking reduction and received higher user ratings (15). We recently published a large NIHR funded trial that showed that a provision of modern refillable EC starter pack is more effective in helping smokers quit than nicotine replacement treatments (NRT), such as patches or chewing gum, including NRT combinations (18% vs 10% sustained validated quit rates at one year) (7). EC and NRT were used within the UK stop smoking service (SSS) and given alongside weekly face-to-face support sessions with stop-smoking advisors.

The trial provided globally important information that was called for by practically all relevant commentaries. The positive result, however, generated the next essential question: *Are modern refillable EC effective without intensive behavioural support?* Only a small minority of smokers attend specialist face-to-face services, even in the UK where such treatment is available locally and free of charge. Although under 5% of smokers attend SSS, the services are important for highly dependent smokers and those exposed to exceptionally high risk of smoking-related illness who need intensive support. Less intensive treatments are likely to be less effective. However, if such treatments can be disseminated on a larger scale and reach more smokers, they can make important contributions to public health.

This RCT will show whether, and to what extent, EC starter packs can help smokers quit when accompanied just by brief weekly telephone support from a helpline, and also whether they work with no further support. We will also include a cost - effectiveness analysis of the interventions and a qualitative sub-study to examine barriers and facilitators to using such an approach by both HCPs who may refer patients to the helpline, and by smokers.

6. Study aims and objectives

6.1 Aims

The proposed research aims to answer three questions:

1) What is the effectiveness and cost-effectiveness of EC provided with no additional treatment compared to the most economical standard care option?
2) To what degree is effectiveness of EC enhanced by telephone counselling via EC-specific helpline and how does this affect the intervention cost-effectiveness?
3) What are the barriers and facilitators to referral by HCPs of smokers interested in EC to an EC helpline, and for smokers using it?

6.2 Primary objective

To assess long-term (6 month) efficacy of electronic cigarettes (EC) with telephone support compared to provision of EC with no ongoing support; and those using using EC without support compared to smokers using free online support (standard care).

6.3 Secondary objective

To compare the study arms in long-term abstinence rates at 12 months and between 6 and 12 months. Self reported 7-day point prevalence abstinence at 4 weeks, 6 and 12 months, cigarette consumption in non-abstainers by vaping status at all time points, frequency and severity of urges to smoke and intensity of 2 cigarette withdrawal symptoms (mouth ulcers and constipation) at 4 weeks, self-reported weight at each time point, respiratory symptoms at each time point, treatment ratings and adherence, adverse reactions to EC, cost effectiveness of interventions, primary and secondary HCPs' and smokers' views of an EC helpline.

6.4 Primary endpoint

CO validated sustained abstinence rates at 6 months post–target quit date (TQD)

6.5 Secondary endpoint

- CO validated sustained abstinence rates at 12 months

- CO validated sustained abstinence rates between 6 and 12 months
- Self-reported 7 day point prevalence smoking cessation at 4 weeks, 6 and 12 months
- Cigarette consumption in non-abstainers by vaping status at four weeks, 6 and 12 months
- Urge to smoke and 2 cigarette withdrawal symptoms (mouth ulcers and constipation) at 4 weeks post TQD
- Self-reported weight at 4 weeks, 6 and 12 months
- Respiratory symptoms at 4 weeks, 6 and 12 months
- Treatment adherence (including EC use at each time point and use of non-allocated products)
- Treatment ratings (e.g. helpfulness)
- Adverse reactions to EC
- Cost-effectiveness of interventions
- Qualitative analysis of HCPs' and smokers' views of EC helpline

Sustained abstinence at 4 weeks, 6 and 12 month post TQD will be defined in accordance with the Russell Standard (17) as a self-report of smoking no more than 5 cigarettes since 2 weeks post-TQD and no smoking in the previous week. At 6 and 12 months this self-report will be validated by a CO reading of <8ppm. In cases where contact or CO validation was not available at the previous contact but abstinence is reported and validated at the subsequent contact, these participants will be included as abstainers. Participants lost to follow-up or not providing any biochemical validation will be included as non-abstainers.

7. Study population

We plan to recruit smokers via both secondary and primary care. Patients will be recruited by Local Clinical Research Networks (LCRN) research nurses (RN) and other HCPs. Participants from primary care will be recruited via mailshots and texts from general practices to smokers on their lists. Participants will also be able to self-refer to the study. We may also recruit through social media, if needed.

7.1 Inclusion criteria

The main trial will recruit adult daily smokers (18 years or over) who are motivated to stop smoking, own a mobile phone, are willing to try either an online and/or texting treatment package or EC with or without telephone support and to receive follow-up calls and are able to read/write/understand English.

The qualitative sub study will recruit health care professionals who treat smokers, participants already taking part in the main study, and smokers not taking part in the main study. The only other inclusion criteria is being able to read/write/understand English.

7.2 Exclusion criteria

For the main trial: Pregnancy and current (at least weekly) use of EC.

There are no exclusion criteria for the qualitative sub study.

8. Study design

We will conduct a three-arm RCT to answer the first two questions and an embedded qualitative study with HCPs and smokers both from within and from outside the trial to answer the third question.

The trial also includes an internal pilot to ensure that it can be delivered as planned, and an economic evaluation.

9. Study procedures

9.1 Identifying participants

RNs and other HCPs in primary and secondary care will identify smokers in inpatient and outpatient settings and inform potential participants about the study. Interested participants will be provided with a patient information sheet (PIS) and give consent for their contact details to be passed to the study team (NB. this is not consent into the study).

Potential eligible participants will also be identified via medical notes by RNs and HCPs in primary and secondary care. They will receive a mailshot or a text from their GP practice/outpatient clinic informing them about the trial and providing an option to access study details and, if interested, to contact the study team via a website or call the team directly.

The social media recruitment, should it be needed, will include the same information. The website will include the PIS and guide interested participants to email the study team directly.

9.2 Informed consent procedure

Potential participants will receive an email/call from the research team after at least 24h to allow time to consider participation. The email will contain the PIS and a link to the study database (REDCap), where participants will give electronic consent, confirm eligibility and complete baseline questions. Participants can request a researcher to contact them to answer any questions or complete the forms by telephone if they prefer. Researchers completing these forms will be GCP trained.

Participants will be emailed or posted a copy of their completed consent form for reference.

Participants who have completed the forms online will then be telephoned by a researcher at a convenient time to be randomly allocated to one of the three study arms. Particpants who have completed the forms over the phone will continue on the phone to be randomised (see Randomisation and blinding section, below). All participants will then receive the appropriate intervention (see Study interventions, below).

Follow-up data (see Measures, below) will be collected at 4 weeks, 6 and 12 months after the TQD. At 6 and 12 months, participants reporting abstinence from smoking will be invited to attend for carbon monoxide (CO) monitoring. Participants attending this session will be given £20 to cover their time and travel expenses.

9.3 Randomisation and blinding

Randomisation (1:1:1) in permuted blocks will be undertaken using a web-based application. There are no stratification factors. As there are 3 treatment groups, the study may use blocks of a minimum size of 9 and a maximum of 18. The trial statistician will produce the randomisation list, which will be embedded into an application that only reveals the next treatment assignment once a participant has been entered into the database. We will use REDCap as the randomisation application which will be hosted by Kings College London (KCL) (a secure system currently used by both Queen Mary University of London (QMUL) and KCL).

Participants who are eligible and consent to take part will be randomly allocated to the experimental or control interventions at baseline. Staff will access the web-based application when the participant is on the phone with them, which will generate a unique participant ID number. The randomisation allocation will immediately be provided by the program and the participant advised of it.

Due to the nature of the trial, the intervention allocation cannot be blinded to participants. We will try to limit expectation effects by recruiting only participants with no strong treatment preference; and by emphasising in the PIS that the relative efficacy of the three treatment options is not known. Staff collecting follow-up data will be blind to treatment allocation until questions are reached that reveal allocation.

10. Schedule for treatment for each visit

10.1 Study interventions

Participants will be randomised to one of three interventions.

NHS Quit Now programme (QN) – control arm: QN is an automated stop-smoking treatment package based on texts and e-mails. It is a part of the NHS web-based Live Well programme to which HCPs would ideally refer all smokers. The website https://www.nhs.uk/live-well/quit-smoking/take-steps-now-to-stop-smoking provides information on health benefits of stopping smoking, advice and resources including local SSS, and an option to enroll in QN. QN sends three or four texts and/or e-mails each day for 28 days with practical advice and motivational messages. Participants will be enrolled in QN by the study team according to their preference regarding texts and/or emails and will select a TQD on which the programme will start. They will be asked not to use EC for at least the first four weeks post-TQD but will be able to follow any other Live Well and QN advice including accessing stop-smoking medications and attending local SSS, as these elements are a part of usual care. Participants can request to stop the texts or unsunscribe to the emails at any time.

***EC starter pack with no ongoing support (EC)*:** Participants will receive instructions on EC use over the phone. It will be explained to them that they will receive a starter pack of refillable EC by post and they will be asked to set up a TQD within a few days of the expected EC delivery. They will be asked to confirm receiving the parcel via text or e-mail, and also to call back if there are problems with the device. Participants not confirming the receipt of the EC will be contacted a week after it was posted to clarify whether it was received. A replacement will be posted if the first does not arrive and the TQD re-set, if required.

Once the starter pack is received, participants will be asked to purchase further EC supplies of their choice themselves. The package will contain the device, USB lead, 5 spare atomisers, two 10ml bottles of e-liquid - (one tobacco and one fruit flavoured, 18mg/ml nicotine), instructions on how to use the EC and advice on sourcing their own future supplies via reputable vape shops or suppliers online.

EC starter pack with helpline support (EC+): Participants will receive the same intervention as the EC arm, but they will also receive 5 supportive phone calls; one on the agreed TQD and then weekly for four weeks. They will also be encouraged to call the helpline if they have any questions and require additional support. The weekly calls will aim to resolve any EC related issues and questions, provide motivational support, and guide participants through the quitting process (call duration will be monitored).

We aim to use a refillable EC that is similar to the type used in the TEC trial (One Kit - Innokin, U.K. Ecig Store), is compliant with UK regulations, and that is not produced by a tobacco company.

We will ask all participants to agree via email/text to a commitment to not use the non-allocated treatment (EC for QN arm and online help for EC arms) for at least the first 4 weeks.

At the end of the study participants will be advised that they can continue with their EC for as long as they want to, but will have to purchase their own EC supplies (this will also be explained at the beginning of the study).

Participants in the QN arm who have not stopped smoking but want to continue trying will be advised to contact their local stop smoking services (or the study staff will refer directly) for ongoing support. They can also continue to access the advice from the NHS QN programme. QN arm non-smokers will also be encouraged to access the QN programme if required and continue with any stop smoking medications they may be using.

10.2 Measures

At baseline:

- Demographic variables, self-reported weight and height (BMI), smoking history
- Fagerstrom Test of Cigarette Dependence (FTCD) (18)
- Mood and Physical Symptoms Scale (MPSS) items relating to urges to smoke and mouth ulcers and constipation only (19)
- European Quality of Life-5 Dimensions questionnaire (EQ-5D-5L) (20)
- Smoking cessation service and health service use
- Respiratory symptoms checklist (RSC) questionnaire (7)
- For QN arm we will record whether participants opted for daily texts, emails or both options

At 4 week follow-up:

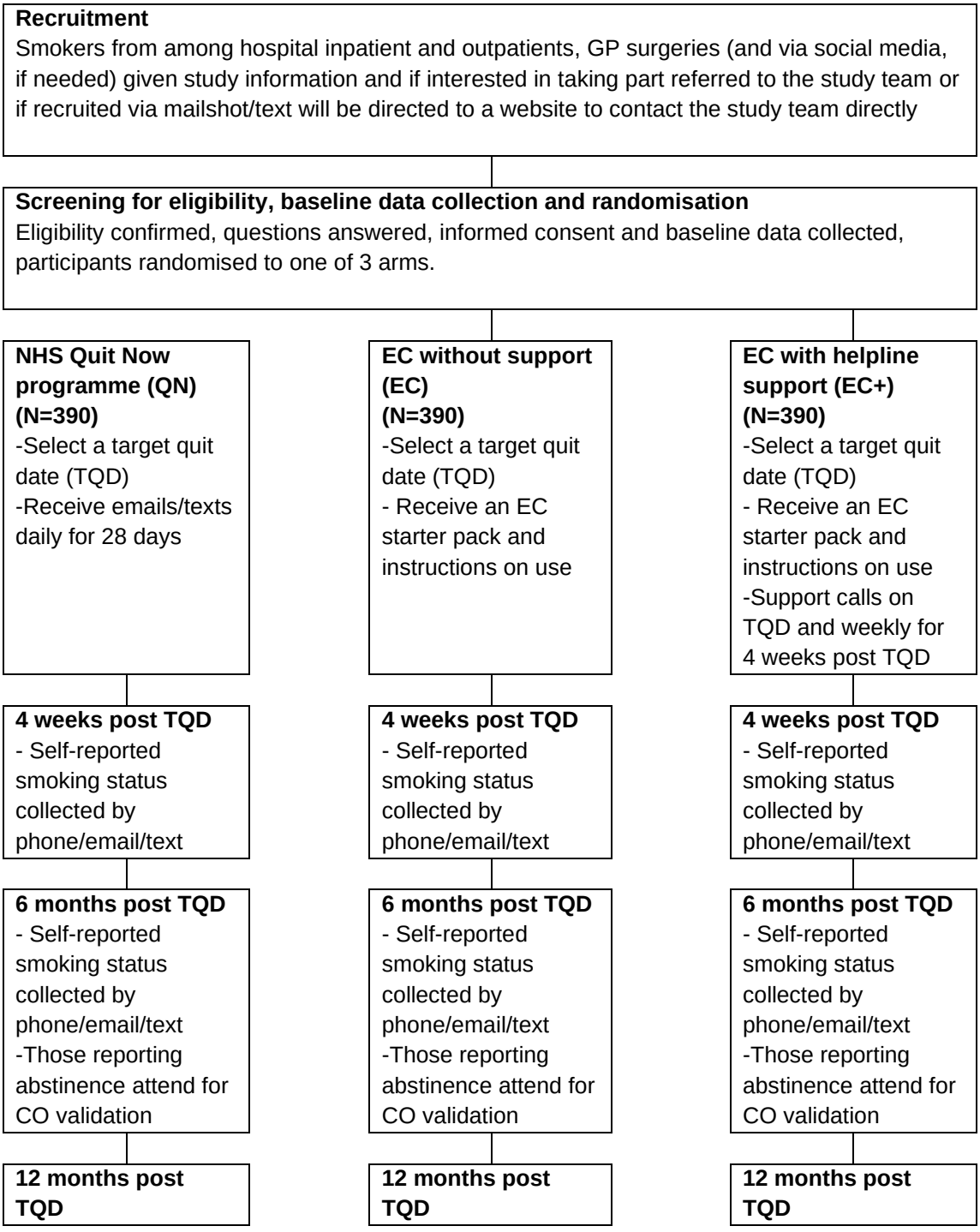
- Smoking/vaping status
- Self-reported weight
- MPSS (urges to smoke and mouth ulcers and constipation only)
- Respiratory symptoms checklist
- Adverse events (AEs)
- Use of QN/EC (For EC: use on days per week, number of weeks used occasionally/regularly and volume of e-liquid/EC cartridges per week; For QN: days per week messages read, visits to the website and use of any of the recommendations)
- Reasons for stopping/reducing use of QN/EC
- Ratings of helpfulness of the interventions and whether participants would recommend it to friends
- Use of non-allocated treatments

At 6 and 12 month follow-up:

- Smoking/vaping status
- Self-reported weight
- Respiratory symptoms checklist
- EQ-5D-5L

- Adverse events (AEs)
- Use of EC (days per week used, number of weeks used occasionally/regularly and volume of e-liquid/EC cartridges per week)
- Reasons for stopping/reducing use of EC
- Smoking cessation service and health service use
- End-expired carbon monoxide reading in self- reported abstainers

10.3 Flow Diagram



- Self-reported smoking status collected by phone/email/text -Those reporting abstinence attend for CO validation **(Analysis N=390)**	- Self-reported smoking status collected by phone/email/text -Those reporting abstinence attend for CO validation **(Analysis N=390)**	- Self-reported smoking status collected by phone/email/text -Those reporting abstinence attend for CO validation **(Analysis N=390)**

10.4 Schedule of Assessment

Measures/ Procedures	**Baseline**	**TQD+4 weeks**	**6 month follow up**	**12 month follow up**
Informed consent	X			
Baseline questionnaire (including demographics, self-reported weight and height (BMI), smoking history and FTCD)	X			
Randomisation	X			
Commitment form	X			
EC starter kit posted (EC and EC+)	X			
Smoking status/CPD	X	X	X	X
CO validation			X (if report abstinence)	X (if report abstinence)
MPSS	X	X		
EQ-5D-5L	X		X	X
Smoking cessation and health service use	X		X	X
Respiratory Health	X	X	X	X
Treatment adherence (use of EC/QN inlcuding quantity/frequency of intervention)		X		
EC/QN ratings		X	X (if LTFU)	
Self-reported weight		X	X	X
Adverse events (AEs)		X	X	X
Use of non-allocated products		X	X	X

10.5 End of Study Definition

The study would be completed and the REC informed after the final attempt to collect 12 month follow-up data from the last randomised participant.

10.6 Subject Withdrawal

Participants will be able to withdraw from the study at any time. Data collected up to the point of their withdrawal will be used in the study analysis and the participants will be included as non-abstainers in the final outcomes.

Participants will be withdrawn if they withdraw their consent to participate. We do not foresee any other reasons to withdraw participants.

10.7 Data Collection and Follow up for Withdrawn Subjects

Participants that do not wish to continue with treatment during the initial period will be followed up at weeks 4, and at 6 and 12 months, unless they do not wish to be contacted.

11. Assessment and management of risk

We do not foresee any risk of taking part in this study. EC are 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, Leicester, 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. There is little doubt they are substantially safer than conventional cigarettes, and they have been shown to increase the rates of smoking cessation.

The benefit of taking part in the study will be providing access to support for current smokers wanting to stop smoking.

12. Statistical considerations

12.1 Sample size

In our TEC trial, the 6-month quit rate in the EC arm was 35%. We estimate this will be reduced to 25% with phone calls replacing face-to-face sessions and to 15% with removing weekly contacts altogether (a recent pilot study recorded 15% validated quit rate with EC starter packs and no further support (21)). The only trial of a social media intervention that included biochemical validation reported 6% 7-day abstinence at six months (22), so we estimate a quit rate of 6% in the QN arm. With these estimates, to obtain 90% power and alpha 0.025 (adjusted for multiple testing, double sided), we need 390 participants to detect the differences between EC+ and EC arms and 286 participants to detect a difference between the EC and QN arms. As per recommended best practice (23), we selected the largest estimate for all three arms (N=390), for the total of 1,170 participants. (Note that in smoking cessation trials, participants lost to follow-up are included as non-abstainers, so there is no sample attrition).

This is the first trial of its kind and the quit rates that we based our power calculations on are estimates derived from the most informative proximal evidence that we are aware of. The trial, however, will have reasonable power to detect differences when the effects are more modest (6% in the QN arm, 12% in the EC arm, and 20% in the EC+ arm), 76% power to detect a difference between QN and EC and 80% for the EC vs EC+ comparison.

12.2 Planned recruitment rate

We will aim to recruit on average 55 participants per month. Recruitment rates will be monitored monthly and additional sites will be recruited if needed. The first six months of the recruitment period will be assigned as an internal pilot to assess recruitment rates and risks of contamination. If the pilot phase is successful, it will also constitute the first six months of the 21-month recruitment period. The table below outlines 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 centres.

	GREEN	**AMBER**	**RED**
Primary criteria – Monthly recruitment rate	Reaches 100% at months 5 & 6	Between 60-100% at months 5 & 6	<60% at months 5 & 6
Outcome	Maintaining this rate will 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).	Rescue plan will be considered by TSC and HTA commissioning board; monitoring visit from HTA; joint decision on whether trial should be modified or continued

As part of the pilot we will also monitor contamination rates, i.e. the QN arm using EC (EC arm use of QN is less likely, but this too will be monitored). Contamination will be defined as any use of EC (even just a puff) daily for five consecutive days within the first four weeks post-TQD in the QN study arm; and any use of QN in the two EC arms. If contamination rate in the QN study arm during the first 4-weeks post-TQD is greater than 20% and remedial actions do not change this by the sixth month of the

pilot, the QN study arm may be terminated. The decision will be made in consultation with the TSC and funder (HTA).

To minimise contamination we will ask participant to agree to the terms of a commitment form, requiring that they do not use non-allocated products in the first four weeks. Participants will be asked to confirm their commitment via a text or e-mail. We used this approach in our previous studies and it is likely to have contributed to very low contamination rates that we had.

We are focusing on contamination risk over the initial 4-week period because product switches later on are most likely in smokers who did not manage to stop smoking with allocated product help. As the primary outcome concerns sustained abstinence from 2 weeks post-TQD, participants who still smoke after this period will be classified as smokers regardless of product treatment use and so any later contamination will not affect the primary outcome result.

12.3 Method of analysis

All analyses will be carried out by the trial statistician.

To describe participants' demographic and smoking characteristics at baseline by arms, descriptive statistics will be presented using mean and standard deviation for continuous measures that are approximately symmetric; median and quartiles if the distribution is skewed. Discrete outcomes will be described using both the number and proportion (percentage). Similarly, summary measures of the primary and secondary outcomes will be presented.

Analyses of abstinence will use intention-to-treat (ITT) principle with participants lost to follow-up or not providing biochemical validation included as non-abstainers/non-reducers (no change in cigarette consumption). However, sensitivity analyses will be conducted to assess the robustness of conclusions to missing outcome data (complete case analysis, multiple imputation) and departures from randomised treatment (per protocol analysis).

In smoking cessation trials, data are not missing completely at 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.

As our analyses focus on two pairwise comparisons (QN vs. EC and EC vs. EC+ arms), we will use a Bonferroni adjustment to account for multiple testing and reduce type I error (alpha = 0.05/2 = 0.025).

12.4 Statistical analysis plan (SAP)

For the primary outcome, the proportion of people remaining abstinent at 6 months will be reported by study arm and compared using a binomial regression with a log

link. This will allow us to estimate the risk ratio. The number needed to treat (95%CI) will also be estimated based on the results of the primary endpoint.

For the secondary abstinence endpoints, we will examine the differences between study arms in the proportions of participants with CO-validated sustained abstinence at 4, 6 months and 1 year. We will compare the frequency of respiratory symptoms at follow-up between study arms while adjusting for baseline. The frequency of adverse events (AEs) and events deemed as adverse reactions to e-cigarettes (ARs) and respiratory symptoms will be compared between arms. The MedDRA coding system will be used for safety information data.

These secondary outcomes are all binary and therefore we will use general linear model with family set as binomial with a log link to estimate risk ratios. If the models fail to converge, we will use general linear model with family specified as binomial with a log link and robust standard errors. If this also fails, we will run a chi-square test and calculate risk ratios (95%CI).

We will also explore differences in the number of cigarettes per day smoked at each follow-up point in non-abstainers and by vaping status using linear regression while adjusting for baseline scores. Similarly, differences in weight at follow-up will be compared at each follow-up using linear regression adjusting for baseline scores. Lastly, urges to smoke and withdrawal symptoms at 4 weeks will be compared by arms while adjusting for baseline scores

Descriptive statistics will be presented to summarise adherence to treatment. For EC use, this will be indexed by whether EC are used at each time point, on how many days per week and the volume of e-liquid per week, and when not used any longer, how long after the TQD the use was stopped. We will also record reasons for stopping use. Types of EC devices and nicotine content and flavours of e-liquids will be recorded at each time point. In the EC+ arm, we will record how many support calls were completed. Regarding QN, we will record whether participants opted for daily texts, e-mails or both, whether they report that they allowed the messages for the full 28-days duration and if not, how long after the TQD they opted out; how many times they report visiting the website; and whether they used any of QN recommendations.

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

Analysis Timeline

Analysis will be carried out in 2 stages. The first stage is an analysis for primary and secondary endpoints once 6 months data collection is complete. This will require a soft data lock of the database. The data will be cleaned and extracted to allow analysis. The database will, nonetheless, remain live to allow collection of 12 month data.

Once the collection of 12 month outcomes are complete, these data will be cleaned and the dataset will be locked (i.e. hard data lock).

13. Qualitative study

An embedded qualitative study will address the third research question: What are the barriers and facilitators to referral by HCPs of smokers interested in EC to the EC helpline, and for smokers using it? The study will involve semi-structured interviews with 20 HCPs and 20 smokers, including HCPs and smokers who were and were not involved in the trial.

13.1 Participants and Recruitment

We propose a quota sampling approach to recruit HCPs in order to capture a range of views and the perspectives of practitioners who would be in a position to refer smokers to an EC helpline in future, should the results of the trial be positive. Following relevant recommendations on sample size in qualitative interview studies (24), a group of 20 HCPs in a variety of different roles, all of whom treat smokers on a regular basis, should be sufficient to obtain a variety of perspectives and identify relevant barriers and facilitators regarding future referral pathways. From within the trial, LCRN research nurses will assist with identifying HCPs at study recruitment sites, provide them with information about the qualitative study and seek consent to pass their contact details onto the research team. If trial recruitment also occurs in primary care, practices involved in the trial will also be informed about the qualitative element and GPs working in the practice will be invited to participate in a short interview. Further recruitment from outside the trial will draw on clinical and practice networks that Professor Bauld (who will lead the qualitative element) is involved in. This includes training workshops she delivers to GPs on cancer prevention in partnership with the Royal College of GPs and Cancer Research UK; collaborations with dental academics and involvement in CPD provision for dentists; and involvement in CPD provision for a range of other HCPs in her role as an Honorary Consultant in Public Health for NHS Lothian.

Twelve participants involved in the study (both smokers and recent ex-smokers) will be recruited. Eight smokers not participating in the trial will be recruited via the UKCTAS tobacco and nicotine discussion group (25), flyers at community venues in London and Edinburgh and, if required, via social media. To facilitate recruitment, a £20 voucher (which cannot be used to purchase tobacco) will be provided regardless of involvement in the study.

HCPs and smokers not involved in the main trial who are interested in taking part will be given a sub study PIS and contact by the research team at the University of Edinburgh to arrange a suitable time to conduct the interview. All main trial participants will be informed about the sub study when they consent to the main

study and will be asked if they are happy to be contacted for an interview if selected. The Edinburgh study team will contact a selection of those who agreed (based on quota sampling) at around 4 weeks post TQD and invite them to take part. Those who are still interested will be emailed the PIS and a convenient time to conduct the interview will be arranged. All sub study participants will give verbal informed consent which will be recorded electronically. Participants will be emailed or posted a copy of their consent form.

13.2 Procedures and Analysis

Semi-structured interview topic guides will be developed for each group of interviewees and piloted prior to use. For HCPs, the interviews will focus on current contact with smokers, existing referral routes, awareness and views regarding EC, mechanisms for referral to an EC helpline if available in future outside of the trial, willingness to refer to an EC helpline and practical issues that may arise. Previous experience suggests HCPs may not consent to long interviews so these will be limited to around 20 minutes. For smokers and quitters, tailored topic guides will be developed to assess their experience of relevant procedures and treatments and their views on EC helpline use. It is anticipated these interviews will take 30-40 minutes. For smokers not involved in the trial the topic guide will focus on willingness to access an EC helpline if available and barriers and facilitators to accessing and using it.

Interviews will be conducted by telephone/Zoom/Skype in most cases to minimise travel costs and to limit any COVID related restrictions but where required and appropriate face to face interviews will be offered. All interviews will be recorded and transcribed. Transcripts will be entered into NVivo 11 and analysis will take an inductive thematic coding approach to explore views and opinions (26).

14. Economic Analyses

A ‘within-trial’ incremental cost-effectiveness analysis will be undertaken using ‘cost-per-quitter’ as used in the primary outcome measure for the trial. The incremental costs and benefits of the treatment arms (EC and EC+) compared with the control arm will be reported using an incremental cost-effectiveness ratio (ICER) where appropriate using 12 month follow up cost and outcome data.

Intervention costs will be prospectively recorded alongside the trial. These include costs of providing EC and the costs of the helpline support service (staff time, costs of maintaining service). We will also record and value the costs of training in the treatment arms, which includes costs outside the other trial arms. We will contact the providers of the Live Well programme to help derive costs of service provision in the control arm. The costs of e-liquid refills paid for by participants will also be recorded.

The Health service use questionnaire will be used to measure participants’ utilisation of wider health care resources in each trial arm at baseline and each follow-up point,

with national average unit costs (27, 28) applied to quantities to derive a health care cost profile. We will use an NHS and PSS perspective as recommended by NICE.

The cost-effectiveness analysis combines intervention costs and wider health care costs with the number of quitters to calculate the cost per quitter of the intervention over and above usual care.

We will also present a cost-utility analysis using cost per QALY within the one year trial period. EQ-5D-5L is administered at baseline and each follow-up to enable to computation of Quality Adjusted Life Years (QALYs) (29) derived by using the area under the curve based on EQ-5D-5L score at each time point (30). We will use the tariff recommended by NICE at the time of analysis to derive health utilities from the EQ-5D-5L responses.

Missing data in smoking status will be treated as per the statistical analysis to keep the results consistent. Missing data in other variables will be handled using multiple imputation imputation assuming missing at random (MAR). The primary analysis will be performed based on imputed dataset following Rubin's rule (31). We will explore the impact of uncertainty with the construction of cost-effectiveness acceptability curves derived by non-parametric bootstrapping for the 'within-trial' analysis (32). The impact of MAR assumption will be assessed in sensitivity analysis.

15. Ethics

The trial will only proceed after obtaining relevant ethical approvals from the National Research Ethics Committee and Health Research Authority (HRA) and it will be conducted in accordance with GCP guidelines. As the trial does not include any investigational medicinal product and the Medicines and Healthcare products Regulatory Agency (MHRA) have previously confirmed to us that EC trials do not require their involvement, MHRA approvals are not required.

16. Public Involvement

The proposal has been discussed with the UK Centre for Tobacco and Alcohol Studies public engagement group of smokers, ex-smokers and vapers (25) (now under the new SPECTRUM consortium). We have sought guidance on the study protocol and development of participant documents. The group will be consulted on the study progress annually about trial progress and results and input will be sought on developing a dissemination strategy for the results.

The project will also be discussed at future annual Stop Smoking Service (SSS) update and supervision events and we will seek input particularly on the qualitative aspect of the study based on advisors' experience.

Two smokers from these panels and an SSS specialist will be invited to join the Trial Steering Committee which will meet during the pilot phase and every 12 months thereafter.

17. Data handling and record keeping

17.1 Data management

Once consented into the study, participants will be given a unique ID number. Once the participant is randomised into the study, they will be assigned a unique randomisation ID number. Both ID's will will be kept on a log.

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

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

17.2 Source data

Data will be recorded directly to a database using online REDCap. We will develop a REDCap database that will provide a secure web application, accessible via HTTPS/SSL, which is fully NHS toolkit compliant. 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.

Elements of the REDCap database will include:

- Consent
- Registration
- Eligibility screening
- Dates
- Randomisation and arm allocation
- Baseline and weekly questionnaires
- Follow-up questionnaires
- AE and SAE forms
- Withdrawal from study
- Study product dispensing

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. Personal identifiable data (PID) will be collected on an instance of REDCap which is fully NHS toolkit compliant, and also stored on a password protected, encrypted file with restricted access to authorised staff only. When the research database is exported for analysis this will be in de-idenitified form, with no PID included.

Surveys will either be completed dicrectly by particpants, or by suitably trained research staff, as designated in the site delegation log, as accurately and completely as possible throughout the study.

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.

17.3 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 General Data Protection Regulation (GDPR) 2018, 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 General Data Protection Regulation (GDPR) 2018 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 online database system). When randomised into the study, each participant will have a unique randomisation number.

Identifiable data will also be collected on an instance of REDCap which is fully NHS toolkit compliant and also stored on a password protected, encrypted file with restricted access to authorised staff only. This is required to allow weekly phone calls and follow-up data collection. This will include name, address, email, telephone number, NHS number and date of birth. Only study personnel, the study sponsor and relevant regulatory authorities will have access to study data. When the research database is exported for analysis this will be in de-idenitified form, with no PID included.

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.

17.4 Record Retention and 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 25 years.

All paper information relevant to the study will be archived and retained for 25 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 database for 25 years, following the sponsors SOP on electronic archiving.

Destruction of essential documents will require authorisation from the Sponsor.

18. Interventions and tools

18.1 Devices

N/A

18.2 Techniques and interventions

See section 10.1 for interventions.

18.3 Tools

We will be using the European Quality of Life-5 Dimensions (EQ5D) (20), Fagerstrom Test of Cigarette Dependence (FTCD) (18), items from the Mood and Physical Symptoms Scale (MPSS) (19) and the Smoking cessation services and health service use questionnaire. All are validated measure used frequently in this are of research. The respiratory questions used to gauge change during treatment have been developed by the research team and have been used to report changes in respiratory outcome in two RCTs.

See section 10.2 for study measures.

19. Safety reporting

19.1 Adverse Events (AEs) and Adverse Reactions (ARs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

An AR is any untoward and unintended response in a participant to an intervention. All AE judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as AR. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

19.2 Notification and reporting of Adverse Events and Reactions

Data on AEs, ARs, SARs and SAEs will be collected. If the AE/AR is **not** defined as SERIOUS, it will be recorded in the CRF and the participant will be followed up by the research team if not resolved. All AEs, ARs and SAEs will be documented in the e-CRF.

19.3 Serious Adverse Events (SAEs) or reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

SARs will be reported to the REC where in the opinion of the Chief Investigator the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

19.4 Investigators Assessment

19.4.1 Seriousness

Adverse event/reactions will be assessed for seriousness according to the definitions given in section 19.3.

19.4.2 Causality

The causality of all serious adverse events/reactions will be assessed in relation to the trial treatment by the CI and study team.

19.4.3 Severity

The severity of the event/reaction will be assessed 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

19.5 Recording of Adverse events or Reactions

The following are considered expected AEs/ARs:
Symptoms which are potentially caused by EC which include; dislike of taste, cough and mouth/throat irritation.

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

19.6 Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be ‘related’ and ‘unexpected’ will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

19.7 Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However, the CI will inform the sponsor and Research Ethics Committee (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

19.8 Notification and Reporting of Serious Adverse Events/Reactions

All SAEs including SARs will be recorded in the subjects’ notes, the CRF, the sponsor SAE form and reported to the co-ordinating site. **Related and unexpected SAE’s should be reported to the sponsor** at research.safety@bartshealth.nhs.uk

within 24 hours of PI or co-investigators becoming aware of the event. Nominated co-investigators can be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites. The original and any subsequent follow-up of SAE Forms must be kept with the investigator site file at the study site.

Additionally related and unexpected SAE's will be reported to the Ethics committee within 15 days.

19.9 Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

19.10 Overview of the Safety Reporting responsibilities

The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

20. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

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 by the co-ordinating site (QMUL) at least once a year.

21. Trial committees

A **Trial Management Group** (TMG) comprising selected co-investigators, and key employed staff will meet as required 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), who will convene during the pilot recruitment phase and every 12 months thereafter. The TSC would be formed of a Chair (Independent), Chief Investigator, study manager, 2 service users (independent), as SSS specialist and an independent statistician.

A Data Monitoring and Ethics Committee (DMEC) will also be convened every 6-12 months, formed of a Chair (independent), independent statistician and independent expert.

22. Finance and funding

The study is funded by the National Institute for Health Research (NIHR).

23. Indemnity

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

24. Dissemination of research findings

The study will be disseminated via conference reports, publications, and if the findings justify this, Public Health dissemination events, as with the previous trial. Our team collaborates with Public Health England (PHE), NHS Health Scotland, Action on Smoking and Health (ASH) and the National Centre for Smoking Cessation Training (NCSCT), among others, and will work with these organisations to disseminate any research findings of interest to key stakeholders. We will ensure that findings are highlighted to the Department of Health and Social Care, devolved governments and health charities, as appropriate.

We will also liase with our PPI expert on assisting with lay dissemination of the study results.

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