Clinical Trial Protocol

Full Title:	**ENHANCE-D: Enhancing Dental Health Advice**
Short Title/Acronym:	**ENHANCE-D**
Protocol Version Number & Date:	**1.0 27th January 2022**

RESEARCH REFERENCE NUMBERS

IRAS Number:	**307071**
EudraCT Number:	**2021-005440-30**
NHS REC Reference:	
ISRCTN References:	

RESEARCH SPONSOR

Sponsor Name:	**The Newcastle upon Tyne Hospitals NHS Foundation Trust**
Sponsor Reference:	**09800**

RESEARCH FUNDER(S)

Funder Name:	**National Institute for Health Research – Health Technology Assessment Programme (NIHR HTA)**
Funder Reference:	**HTA NIHR129780**
NIHR funder statement.	**This project is funded by the National Institute for Health Research (NIHR) HTA Programme [Project reference number NIHR129780]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.**

Statement: This protocol has regard for the HRA guidance.

PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures 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 trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: **ENHANCE-D: Enhancing Dental Health Advice**

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I have carefully read and understood protocol version 1.0. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

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TRIAL SUMMARY

Trial Title	ENHANCE-D: Enhancing Dental Health Advice	
Acronym	ENHANCE-D	
Summary of Trial Design	A pragmatic, multi-centre, definitive, open label, 3 arm, parallel group, individually randomised controlled, superiority trial, comparing the clinical- and cost-effectiveness, and safety of enhanced smoking cessation interventions to usual care, and each other (with an internal pilot).	
Summary of Participant Population	Adult regular tobacco smokers attending an NHS dental setting	
Planned Sample Size	1460 participants 455 Periodontitis subgroup	
Setting	56 NHS primary dental care settings across 7 UK regional hubs	
Interventions	VBA: usual care (control) Nicotine Replacement Therapy (NRT): standard 12-week course of combination NRT with single-visit behavioural support E-cigarette (EC) starter kit with single-visit behavioural support	
Follow Up Duration	6 months for periodontal health parameters and 12 months for smoking outcomes	
	Objectives	**Outcome Measures**
Primary	To compare smoking abstinence at 6 months of NRT and EC to usual care and to each other (all participants).	• Biochemically verified smoking abstinence at 6 months
Key Secondary	To compare the periodontal health at 6 months of NRT and EC interventions to usual care and to each other, for those with periodontitis at baseline (the trial is powered to answer this key secondary objective definitively).	• Percentage of periodontal sites at 6 months with PPD (Pocket Probing Depths) ≥5 mm

Secondary	To evaluate other parameters of oral health including oral health-related quality of life. To evaluate nicotine dependence, urges to smoke, withdrawal symptoms and longer term smoking abstinence (12 months). To assess costs and benefits in the form of a cost-effectiveness analysis and cost-benefit analysis of NRT and EC in comparison to usual care at 6 months. To estimate participants' preferences for each of the interventions in monetary units using a contingent valuation study. To compare the adverse event profiles of the interventions. To confirm the acceptability of these interventions and explore experiences.	• Expired air Carbon Monoxide (eCO) • Continuous biochemically verified smoking abstinence at 12 months • Fagerstrom Test for Nicotine Dependence (FTND) • Mood and Physical Symptoms Scale (MPSS) • Oral Health Quality of Life Assessment (OHQoL-UK) • Number of teeth • Costs to the NHS and participants • Incremental cost per smoking abstinence • Net monetary benefits based on participants' willingness-to-pay for the intervention and associated outcomes • Incremental net benefit **<u>Periodontitis subgroup only</u>** • Gingival Index [Lobene Modified Gingival Index] • Plaque Index [Silness and Loe plaque index] • CAL (Clinical Attachment Loss) • BOP (Bleeding on Probing) • CODS- Clinical Oral Dryness Score • PESA (Periodontal Epithelial Surface Area) • PISA (Periodontal Inflamed Surface Area)
Sub-study objective	To assess socioeconomic inequalities in trial participation, intervention fidelity, and outcomes. Led by Prof. Conway (University of Glasgow)	
Investigational Medicinal Product(s)	Nicotine replacement therapy N.B. As per MHRA guidance e-cigarettes have not been identified as a IMP (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/614813/CTA_MOCK_Examples.pdf)	
Formulation, Dose & Route of Administration	Combination NRT to include a nicotine transdermal patch plus either nicotine chewing gum or nicotine lozenge. An initial 4-week supply followed by 8-week supply if required. <u>Nicotine transdermal patches</u> Option 1: NiQuitin 7 mg, 14 mg, 21 mg [24-hour patch] Option 2: Nicorette invisi 10 mg, 15 mg, 25 mg [16-hour patch]	

	Nicotine chewing gum Nicorette gum 2 mg, 4 mg Nicotine Lozenges Nicorette lozenge 2 mg, 4 mg
Consumer product	E-cigarette starter kit Stainless Steel Aspire PockeX e-cigarette, coil replacement pack, 3-pin plug, 10 x Halo standard 10ml e-liquids (4 flavour options available)

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GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
3A	Ask, Advice, Act
AE	Adverse Event
AR	Adverse Reaction
BOP	Bleeding on Probing
CA	Competent Authority
CAL	Clinical Attachment Loss
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CI	Chief Investigator
CODS	Clinical Oral Dryness Score
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DH	Dental Hygienist
DN	Dental Nurse
DSUR	Development Safety Update Report
DT	Dental Therapist
EC	E-cigarette
eCO	Expired air Carbon Monoxide
EudraCT	European Clinical Trials Database
FTND	Fagerstrom Test for Nicotine Dependence
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

GI	Gingival Index
GP	General Practitioner
HRA	Health Research Authority
HTA	Human Tissue Authority
HTAct	Human Tissue Act
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
JLA PSS	James Lind Alliance Priority Setting Partnership
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MGI	Modified Gingival Index
MPSS	Mood and Physical Symptoms Scale
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NRT	Nicotine Replacement Therapy
OHQoL-UK	Oral Health Quality of Life Assessment
OPMD	Oral potentially malignant disorders
PESA	Periodontal Epithelial Surface Area
PI	Principal Investigator

PIn	Plaque Index
PIS	Participant Information Sheet
PISA	Periodontal Inflamed Surface Area
PK	Pharmacokinetic
PPD	Pocket Probing Depths
QA	Quality Assurance
QALY	Quality-adjusted life year
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSS	Stop Smoking Service
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
VBA	Very Brief Advice
WTP	Willingness-to-pay

1. BACKGROUND AND RATIONALE

The problem and existing evidence

Smoking and oral health

Smoking is a major contributor to health inequalities [1] and oral health inequalities persist across the UK with those from the lowest socioeconomic groups bearing the greatest burden of disease [2]. Dental practices have a wide population reach which provide opportunities to impact on inequalities.

Periodontitis is the sixth most prevalent health condition in the world. Severe periodontitis affects approximately 10% of UK adults and is a leading cause of tooth loss in adults.[3] Consequences of periodontitis include bleeding gums, tooth mobility, tooth loss and reduced quality of life. There is evidence of an association with diabetes, cardiovascular disease and adverse pregnancy outcomes. Smoking is the biggest risk factor for periodontitis development and its progression; smokers have poorer responses to periodontal treatment.[4] Such is the impact of smoking on treatment, that it has been suggested that dentists should focus on smoking cessation as a primary treatment strategy for periodontitis, rather than on conventional therapies.[5]

In 2016 there were 7200 cases of oral cavity (mouth) or oropharyngeal (throat) cancer in the UK.[6] Smoking is estimated to be responsible for up to 75% of these.[7] Quitting smoking has been shown to reduce oral cancer risk, reducing to levels of never smokers after 20 years.[8]

Smoking cessation interventions in dental settings

Although there is evidence that smoking cessation leads to improvements in oral health and treatment outcomes [4, 8] there is less evidence about how best to support smokers to achieve cessation in dental settings. A Cochrane review of smoking cessation interventions by dental professionals found that they may be effective but they were unable to make specific recommendations regarding intervention components due to large heterogeneity between studies.[9]

In the UK, dental professionals (dentists, dental hygienists [DH], dental therapists [DT] & dental nurses [DN]) are expected to provide Very Brief Advice (VBA) smoking cessation interventions, designed to be delivered in under 30 seconds, following the 3A approach (Ask, Advise, Act), typically resulting in signposting to a local pharmacy, Stop Smoking Services (SSS) or General Practitioner (GP).[10] Often there is no formal pathway for referral or follow up; in a recent survey by our group only 17% of dental professionals reported completing referrals.[11] This is exacerbated by the variable access to SSS across the country.[12] In medical settings, VBA interventions typically increase the quit rate at 6 months from 3 to 5% (RR 1.66).[13] Further improvement is seen in quit rates with more intensive behavioural support and the addition of pharmacotherapy.[14, 15] Hence, the current approach of providing VBA in the dental setting is potentially a missed opportunity and there is considerable scope for enhancing the smoking cessation support offered. This is particularly true given that large proportions of the population attend the dentist on a regular basis. For example, in Scotland, 94% of the population is registered with a dentist (98% in the most deprived areas) with 70% visiting in the last 2 years.[16] There are also often smoking-related oral changes (e.g. tooth staining, mucosal changes, gum recession and tooth looseness/ loss) that can be used as powerful prompts for a quit attempt ('teachable moments').

ENHANCE-D aims to address this, building on existing evidence by evaluating the clinical- and cost-effectiveness and safety of two enhanced interventions, Nicotine Replacement Therapy (NRT) or an

E-cigarettes (EC) starter kit, each combined with a single-visit behavioural intervention, in NHS primary dental care settings.

E-cigarettes

ECs are the most common quit aid in the UK, with around 4 out of 10 smokers reporting using ECs in their most recent quit attempt.[17] There is growing evidence of their effectiveness for smoking cessation [18, 19] although there is currently an evidence gap in non-specialist real world settings such as dental settings. Recently, a well-conducted NIHR-funded randomised controlled trial (RCT) examined the effectiveness of ECs compared to standard NRT within the UK SSS,[19] concluding that ECs were more effective than NRT. The trial population were dependent smokers, with high rates of social disadvantage, who were motivated to quit and who received expert specialist support. The authors concluded that further studies should investigate broader populations and outside of the SSS (which was only accessed by around 4% of smokers in 2017/2018 [20]). Our proposal builds on this trial[19] by investigating ECs in a pragmatic real world setting i.e. non-specialist providers, offering EC starter kits to smokers attending a dental practice, regardless of their intention to quit. The findings will therefore have applicability beyond dentistry and will contribute significantly to the evidence base on ECs.

Evidence is also needed on ECs' effect on oral health and treatment outcomes. A national US review stated there was only limited evidence that 'switching to ECs will improve periodontal disease in smokers'.[21] Varying recommendations on ECs have been provided by dental professional bodies, likely contributing to mixed opinions among dental professionals. This was demonstrated in a recent survey[11] conducted by our team in which a third of respondents were of the opinion that ECs were equally or more harmful for health than tobacco cigarettes, against the current evidence base.[21-23]

Nicotine Replacement Therapy

There is high-quality evidence that NRT, particularly combination NRT, is effective in general populations motivated to quit.[15, 24] However, as identified in the dental Cochrane review[9] there is less evidence to support the use of NRT in dental settings and no studies conducted in UK primary dental care. The review[9] identified 3 studies which used NRT: Binnie et al.[25] was 'preliminary' in design, conducted in tertiary dental care and called for a multi-centre RCT to be conducted, Gordon et al.[26] did not comply with current smoking outcome measure recommendations[27] (no biochemical verification); and Hanioka et al.[28] was a small (n=56) trial with no reported sample size calculation, conducted in Japan using intensive behavioural support (average 116 min) with NRT. No new studies were identified as part of the ongoing update.

Although the results of ENHANCE-D are unlikely to change the outputs/conclusions of the NRT Cochrane reviews[15, 24] they would be highly likely to change the 'dental setting' Cochrane review[9].

NRT is also being used as an active comparator for the EC intervention in this trial as recommended by our patient advisory groups, the James Lind Alliance Priority Setting Partnership (JLA PSP)[29] and in the NIHR commissioned call.

Potential impacts on patients and the NHS

Providing effective and cost-effective smoking cessation interventions through dental professionals will potentially have significant positive impacts on both the general health and oral health of our patients and help reduce health inequalities in the population.

The NHS offer of smoking cessation support in dental settings could be substantially changed by this trial. This supports the NHS Long Term Plan which called for 'more NHS action on prevention and health inequalities', identifying smoking as the largest modifiable risk factor. The Plan indicates that over a million people per day have contact with the NHS, at 'moments in their lives that bring home the personal impact of ill health'. Smokers attending a dental practice, especially those with periodontitis, exemplify those experiencing a teachable moment in which the NHS can do more through enhancement of its current smoking cessation offer. Data shows that approximately 22% of dental patients are smokers.[3, 30]

In summary, the ENHANCE-D trial proposal is an urgently required piece of research that will inform policy and practice, with significant potential to improve the general and oral health of our patients and reduce inequalities. Although focused on the UK, the results will be equally important internationally, where research of this type is difficult to conduct due to differing policy and practice contexts or lack of funding for research involving ECs.

The aim of the proposed trial is to compare the clinical- and cost-effectiveness and safety of three smoking cessation interventions delivered by dental professionals in NHS primary dental care.

The trial is designed to answer the question: Is the offer of standard NRT or an EC starter kit, by a dental professional, an effective, cost-effective and safe aid to help smokers attending a dental practice to stop smoking, compared to usual care (VBA) and, for those with periodontitis, does this lead to improved outcomes of periodontal therapy?

2. OBJECTIVES AND OUTCOME MEASURES

2.1. Primary Objective

To compare biochemically verified smoking abstinence at 6 months of NRT or EC interventions compared to usual care (all participants).

2.2. Secondary Objective(s)

The key secondary objective is to compare the periodontal health at 6 months of NRT or EC compared to usual care, for those with periodontitis at baseline (the trial is powered to answer this secondary objective definitively).

Other secondary objectives include assessing a number of quantitative and qualitative outcomes such as smoking abstinence at 12 months, oral health outcomes (for those with periodontitis), cost-effectiveness, patient quality of life, acceptability and associated experience of the patients and dental professionals.

2.3. Outcome Measures

The following outcomes will be measured and reported.

2.3.1. Primary Outcome

Biochemically verified smoking abstinence at 6 months (an established measure of long-term smoking abstinence).

2.3.2. Secondary Outcomes

2.3.2.1. Key Secondary Outcome Measure

Periodontitis subgroup: Percentage of periodontal sites at 6 months with PPD (Pocket Probing Depths) >=5 mm (a standard outcome measure of periodontal health for periodontal studies).

2.3.2.2. Secondary Outcome Measures

The following outcomes will be measured in all the participants:

- Adverse events (shortness of breath, cough, phlegm, nausea, throat/mouth irritation, sleep disturbance, headache, mouth dryness, dizziness/feeling faint)
- Continuous biochemically verified smoking abstinence at 12 months (a long term measure of smoking abstinence)
- Fagerstrom Test for Nicotine Dependence (FTND), a measure of degree of dependence among smokers coming to a smoking cessation clinic
- Mood and Physical Symptoms Scale (MPSS)
- Oral Health Quality of Life Assessment (OHQoL-UK)
- Expired air Carbon Monoxide (eCO; for patients who attend follow-up visits)
- Number of teeth
- Costs to the NHS and participants
- Incremental cost per smoking abstinence
- Net monetary benefits based on participants' willingness-to-pay for the intervention and associated outcomes
- Incremental net benefit
- Qualitative evaluation
- An analysis of socioeconomic status will be carried out as part of a related sub-study.

The following outcomes will be measured in the **periodontitis subgroup only:**

- GI (Gingival Index [Lobene Modified Gingival Index]; a measure of gingival health)
- PI (Plaque Index [Silness and Loe plaque index]; a measure of oral hygiene)
- CAL (Clinical Attachment Loss; a measure of current and previous periodontal disease exposure)
- BOP (Bleeding on Probing; a measure of gingival health)
- CODS- Clinical Oral Dryness Score
- PESA (Periodontal Epithelial Surface Area; a novel method of measuring periodontal health)
- PISA (Periodontal Inflamed Surface Area; a novel method of measuring periodontal health)

3. TRIAL DESIGN

This trial is a pragmatic, definitive, 3 arm, parallel group, individually randomised controlled, superiority trial, including an internal pilot. Participants will be randomised in a 1:2:2 ratio between usual care (VBA) and the two interventions (standard NRT or EC starter kit), stratified by baseline periodontal status and regional hub.

The participants will be adult regular tobacco smokers attending NHS dental settings.

Internal Pilot

ENHANCE-D will have an internal pilot designed to assess a range of parameters. The duration will be 8 months, from the start of the recruitment period, based on when we predict to have recruited 25% (n=365) of the participants and have all sites open. Progression criteria are detailed below:

Progression criteria	**Red % (n)**	**Amber % (n)**	**Green %(n)**
Total number of participants recruited	<50% (182)	50-99% (183-364)	≥100% (365)
Number of sites opened as % of expected	<50%	50-99%	100%
Proportion of recruited participants who are in the periodontitis subgroup	This information will be used to determine if any additional recruitment steps need to be taken to ensure recruitment to the periodontitis subgroup.		

4. TRIAL SETTING

This trial will be completed in NHS dental settings (primary care) across 7 research regions (Dundee, Edinburgh, Glasgow, Newcastle, Sheffield, Birmingham and Plymouth), representing a diverse population across two countries with different NHS payment systems.

5. ELIGIBILITY CRITERIA

Only personnel formally delegated by the Principal Investigator to assess eligibility may perform this task and this assessment must be documented in the participant's dental notes.

5.1. Inclusion Criteria

All participants:

- Aged at least 18 years old
- Current regular smoker
- Willing and able to provide informed consent prior to any trial procedures taking place
- A basic Periodontal Examination (BPE) completed within the last 3 months.

Periodontitis subgroup:

- Minimum of 16 natural teeth (excluding third molars)
- Diagnosis of periodontitis stage II (or greater), grade A/B/C and currently [i]unstable [31](As diagnosed by the primary care dentist/hygienist/therapist)

5.2. Exclusion Criteria

- Pregnant or breastfeeding
- Enrolled in another interventional research trial which could affect the outcome of this trial
- Having used an aid to quit smoking or reduce/quit alcohol in the week prior to enrolment
- Phaeocromocytoma, uncontrolled hyperthyroidism, extensive dermatitis/skin disorder
- Taking one or more of the following medications:
    - Clozapine
    - Olanzapine
    - Theophylline
    - Aminophylline

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

6. TRIAL PROCEDURES

6.1. Recruitment

1460 participants will be recruited for this trial. Dental practices are very variable in their set up and hence our recruitment strategy will be flexible in line with the pragmatic design of this trial.

6.1.1. Patient Identification

There are two main recruitment options:

a) Identified via screening

Potentially eligible patients will be identified prior to their planned dental visit by examining dental records. The participant information sheet will be provided prior to their appointment e.g. posted paper version or texted/emailed link to online version. The patient will be given sufficient time to consider their participation in the trial and allowed the opportunity to discuss the trial. Additional time will be planned for the visit. At the dental visit, a delegated member of the site team will obtain informed consent and confirm eligibility. Randomisation will be completed, and the appropriate interventions delivered.

b) Opportunistic identification

Potentially eligible patients will be identified during attendance at their dental visits. In the vast majority of cases a two-visit approach will be taken, where the dental professional will establish eligibility, introduce the trial and provide the trial information at their routine visit. A second visit will be arranged in order to obtain informed consent, randomisation and

delivering the interventions. In some cases, it may be preferable to complete all the processes in a single visit.

In both cases, interventions will be shipped to participants, which will take at least 24 hours. Should the participant decided to withdraw from the trial within this period they would inform the research team and return or dispose of the NRT/EC.

A screening log will be kept which will include details of all patients who are considered for trial participation. This log will include the reason that any patient did not take part, if applicable. Un-identifiable data (year of birth, sex, and postcode) from the screening log will be entered into the trial database.

6.1.2. Patient identification for the periodontitis subgroup

The primary care dental professionals will identify patients who are eligible for the periodontitis subgroup whilst establishing eligibility for the main trial. These participants will receive a PIS specifically for the sub group. If a potentially eligible patient is identified, then contact will be made with the local hub team to arrange for baseline oral health data to be collected. These should be collected before (or on the same day) as the interventions are delivered.

6.2. Consent

The Participant Information Sheet and Informed Consent Form will be given to potential participants when approached to take part in the trial. They will have the opportunity to discuss the trial in more detail and the implications of the protocol, and any risks involved in taking part, with a member of the research team. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Potential participants will be allowed time to consider the information, and will have the opportunity to discuss any questions, with the Investigator, to decide whether they will participate in the trial. Written Informed Consent will be received by means of initialling to confirm agreement of each consent statement followed by participants name, date and signature and the person who receiving the informed consent will then provide their dated signature. The person who received the consent must be trained and have been authorised to do so by the Principal Investigator (PI) on the delegation log.

The participant will be asked to provide optional consent to take part in the qualitative sub study. See section 15 for more details.

The original signed consent form will be retained in the Investigator Site File (ISF), with a copy provided to the participant and a copy filed in the participant's dental records. Consent to continue with trial participation will be checked verbally at each trial visit and documented in the participant's dental notes.

6.3. Randomisation

Following completion of informed consent and confirmation of eligibility participants will be randomised to receive VBA, NRT or EC starter kit, in a 1:2:2 ratio using random permuted blocks within strata. Randomisation will be stratified by regional hub (7 levels) and by baseline

periodontal status (3 levels: all sextants BPE code ≤2, 1-3 sextants with BPE code 3 or 4, ≥4 sextants with BPE code 3 or 4).

Randomisation will be performed by a member of site staff, appropriately trained and identified on the delegation log, using the Sealed Envelope™ system (a secure, central, 24-hour web-based randomisation system with concealed allocation).

6.4. Blinding

Prior to randomisation participants will be blinded to the purpose of the trial and will not be aware of the treatment interventions being offered. The trial will be described in terms of different packages of advice that the dental team can offer rather than detailing the interventions in detail (VBA, NRT, EC). Prior to randomisation the participants will be unaware that the specific aim of the trial is smoking cessation.

This is a common approach in research studies where some of the interventions are light touch, such as the brief intervention (control group) in this trial. This is done because by explaining the interventions in the PIS, you have effectively delivered the intervention. Similar approaches have been used in a range of studies [32-34], including a recent smoking cessation study [35]. The PIS will detail that if any 'medication or other devices' are offered by the dental professional, that the participant can decide not to use these, but if they do, any side effects, benefits and risks will be discussed by the dental professional to inform the participants decision.

For the primary outcome (biochemically verified smoking abstinence at 6 months) assessors will not be blinded to participant allocation or smoking status but an objective measure will be taken to verify self-reported tobacco abstinence (expired air carbon monoxide, eCO). For the key secondary outcome (percentage of periodontal sites at 6 months with PPD≥ 5mm) the outcome assessors will be blinded to participant allocation and smoking status. Participants will be asked not to disclose their smoking status or methods of smoking cessation to the blinded outcome assessor. Due to the unequal randomisation allocation ratio (1:2:2) it will be impossible to fully blind the trial statisticians because the group sizes will identify the usual care control group (VBA) or active groups. The statisticians will remain partially blind, they will not know which 'active' group is which (NRT or EC).

6.5. Baseline Assessments & Data

The assessments collected at baseline are summarised in the Schedule of Events (6.11). Detailed breakdown of these assessments are provided below.

Assessments for all participants;

- **Demographics**
  a) Age
  b) Sex
  c) Ethnicity
  d) Home postcode
  e) Highest level of educational level obtained
  f) Job title, or reason for not working
  g) Receipt of low-income benefits

- **Medical/ Smoking History**
    - Type of tobacco used (factory made cigarettes, hand rolled cigarettes, cigars, pipes)
    - Current amount of tobacco/day (cigarettes/day or weight of tobacco/day)
    - Total pack years
    - Any previous quit attempts. Date of last attempt
    - Any previous use of NRT and EC
- **Fagerstrom Test for Nicotine Dependence (FTND)**

  This tool assesses the degree of dependence among smokers coming to a smoking cessation clinic and is extensively used in tobacco research [40]. It consists of a set of six questions, giving a score of 0-10 with higher scores representing heavier smokers.

- **Mood and Physical Symptoms Scale (MPSS)**

  This 12-item questionnaire assesses cigarette withdrawal symptoms. Each item gives a maximum score of 5 giving a total maximum score of 60. Ten of the items have a minimum score of 1 and two have a minimum score of 0, giving an overall minimum score of 10. A higher score indicates worse withdrawal symptoms. It has been used for over 30 years with its psychometric properties being assessed by West and Hajek, 2004. To assess the effect of abstinence you can calculate the change from baseline (just prior to stopping smoking) to the post-abstinence follow-up point for items 1. to 7. and 10. to 12., and take the raw scores for items 8 and 9 [41]. To compare abstinence symptoms under two or more conditions (i.e. the two arms of this trial) these scores can be compared or instead the post-abstinence ratings compared using the baseline ratings as covariates (i.e. instead of subtracting them). This method gives slightly more power to detect differences. The ratings will be analysed individually but also totalled together to give a composite score (MPPS Total).

- **Oral Health Quality of Life Assessment (OHQoL-UK)**

  The OHQoL-UK questionnaire [42] will give a measurement of oral health related quality of life at two points in the trial (baseline and 6-months). The 16 items allow responses in either a positive or negative (bidirectional) manner to a series of statements about the effect of oral health on specific aspects of respondents' daily lives. The responses range from "very bad" (score 1) to "very good" (score 5). Responses are then summed to give a total score out of 80, or can also be summed within three sub-domains (physical, social and psychological) as described by McGarth and Bedi [43]. The lower the score the poorer the OHRQoL.

- **Number of teeth**

  The number of teeth present will be recorded from the latest dental charting on the dental records (i.e. no additional examination will be conducted).

Assessments for the periodontitis sub group only – *conducted by the regional blinded hub assessors;*

- **Clinical Oral Dryness Score (CODS)**

  Oral dryness (xerostomia) will be measured using a 10 point scale as described by Osailan et al [38]. A score of 1 is assigned for each of the following:

1) mirror sticks to buccal mucosa;

2) mirror sticks to tongue;

3) frothy saliva;

4) no saliva pooling in floor of mouth;

5) tongue shows loss of papillae;

6) altered/smooth gingival architecture;

7) glassy appearance of other oral mucosa, especially palate;

8) tongue lobulated/fissured;

9) active or recently restored (last 6 months) cervical caries (>2 teeth); and

10) debris on palate (excluding under dentures).

- **Gingival Index (GI [Lobene Modified Gingival Index])**

  A full mouth gingival index will be recorded based on the Lobene Modified Gingival Index [36] (MGI) rated on a scale of 0 to 4 (recorded at 6 sites per tooth):

0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in texture of any portion of but not the entire margin or papillary gingival unit
2	Mild inflammation; but involving entire margin or papillary unit
3	Moderate inflammation; glazing, redness, oedema and/or hypertrophy of margin or papillary unit
4	Severe inflammation; marked redness, oedema and/or hypertrophy of marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration]

- **Plaque Index (PIn [Silness and Loe plaque index])**

  The plaque index of Silness and Loe [37] will be employed to measure plaque (without disclosing) at 6 sites per tooth.

  Scores will be assigned as follows:

0	No plaque
1	A thin film of plaque at the gingival margin which may be seen only after running the probe along the tooth surface
2	Moderate accumulation of plaque deposits which can be seen with the naked eye
3	Extensive accumulation of plaque deposits

- **Gingival recession (used to calculate CAL outcome measure)**

  Gingival recession will be recorded to the nearest millimetre using a manual UNC-15 periodontal probe. Gingival recession is the distance from the free gingival margin to the cemento-enamel junction. Gingival recession will be indicated as a positive number and gingival overgrowth will be indicated as a negative number.

- **Pocket Probing Depths (PPD)**

  A trained and calibrated hygienist, blinded to group allocation, will collect the PPDs using a manual UNC-15 periodontal probe to record the probing depths to the nearest millimetre. Probing depth is the distance from the probe tip (assumed to be at the base of the pocket) to the free gingival margin. Recorded at 6 sites per tooth.

- **Bleeding on Probing (BOP)**

  Following probing, each site will be assessed for bleeding on probing, if bleeding occurs within 10s of probing, a score of 1 will be assigned for the site, otherwise, a score of 0 will be assigned. Recorded at 6 sites per tooth.

- **Periodontal Epithelial Surface Area (PESA)**

  PESA quantifies the root surface area affected by attachment loss. It is calculated from the PPDs using the technique described by Nesse 2008.[39]

- **Periodontal Inflamed Surface Area (PISA)**

  PISA quantified the surface area of inflamed periodontal tissue. It is calculated from the PPDs and BOP data using the technique described by Nesse 2008.[39]

- **Biological sample collection**

  Subgingival dental plaque will be collected from 10 periodontal pockets (ppd ≥ 5mm) using sterile paper points and pooled. If less than 10 pockets are available, then as many as possible will be used. The same sites will be used at both collection visits. If a site is not available at the 6-month visit, due to tooth extraction, no additional sites will be added. Samples will be stored dry and shipped to Newcastle University where they will be stored at -80°C until analysis.

  Oral epithelial cell samples will be collected using buccal brush biopsies. Cells will be stored in RNA protection reagent and shipped to the laboratory for RNA extraction. The presence of oral potentially malignant disorders (OPMDs) at the site where the buccal brush biopsies are collected will be recorded.

- **Exploratory biological sample collection**

  Unstimulated saliva will be collected in the periodontitis subgroup at selected hub locations. This will be collected by drooling into a collection vessel until approximately 5ml has been collected (estimated to take 5-10 minutes). Participants will be asked if they have eaten, drank, taking medication or performing oral hygiene tasks in the hour prior to collection. Samples will be frozen on return to the hub base.

Calculus samples will be collected in the periodontitis subgroup at selected hub locations. Samples will be frozen on return to the hub base.

6.6. 7 days after ordering trial products

Participants randomised to NRT or ECs will be contacted by phone call or SMS message by the site staff to confirm they have received the trial products.

6.7 Day 21 (NRT Arm only)

Participants randomised to NRT will be contacted via phone call to arrange an additional 8 week re-supply if appropriate. Orders will then be placed with Newcastle Pharmacy Specials.

6.7. Day 28

Participants randomised to NRT will be given a phone call or SMS message by the site staff to confirm they have received the trial products.

All Participants will be contacted by phone to record any adverse events and any concomitant medication taken for any pre-specified AEs.

6.8. 6 Month follow-up

All participants;

- **Self-reported smoking status**

  The smoking status including type and amount will be recorded.

- **Expired air Carbon Monoxide**
  In accordance with national guidelines [27], the trial will measure eCO on all participants at 6-months and 12-months. A carbon monoxide monitor will be used.
- **Fagerstrom Test for Nicotine Dependence (FTND)**
- **Mood and Physical Symptoms Scale (MPSS)**
- **Oral Health Quality of Life Assessment (OHQoL-UK)**
- **Number of teeth**
- **Health service utilisation questionnaire**
- **Adverse events and concomitant medication for AEs.**

Periodontitis subgroup only;

- **Periodontitis therapy**

  See section 7.16 for the details we will be recording

- **Clinical Oral Dryness Score (CODS)**
- **Gingival Index (GI [Lobene Modified Gingival Index])**
- **Plaque Index (PIn [Silness and Loe plaque index])**
- **Gingival recession (used to calculate CAL outcome measure)**
- **Pocket Probing Depths (PPD)**

- **Bleeding on Probing (BOP)**
- **Periodontal Epithelial Surface Area (PESA)**
- **Periodontal Inflamed Surface Area (PISA)**
- **Sub gingival dental plaque**
- **Buccal brush biopsy**
- **Unstimulated saliva (exploratory data collection in selected sites only)**
- **Calculus collection (exploratory data collection in selected sites only)**

6.9. 12 Month follow-up

- **Expired air Carbon Monoxide**
- **Adverse events**

The Schedule of Events (6.11) details the assessments to be completed at each time point.

For those participants who fail to attend the six-month or 12-month follow-up visit a member of the site research team will attempt to contact via telephone or SMS message and establish self-reported smoking status and any adverse events. For those who report being abstinent, a saliva collection kit will be sent out which will test for cotinine and anabasine. This will allow us to verify self-reported smoking status of those who have abstained from all nicotine, those using only NRT/ECs and those still smoking burnt tobacco. Sending saliva sample kits by post with instructions on how the correctly use the kit, and with a prepaid return envelope, has been successfully used in several other studies for remote validation of smoking status. One reminder phone/SMS will be used if the kit is not returned within 10 days. In addition, if the carbon monoxide monitor fails or is unavailable a salvia sample can be taken.

6.10. Smoking abstinence definition

eCO

A reading of 10 parts per million (ppm) or above signifies smoking tobacco.

Salivary assessment

Saliva samples will have biochemical validation for cotinine and anabasine. Cotinine is a metabolite of nicotine and salivary cotinine is a biomarker of nicotine exposure and will give high readings in those using burnt tobacco, e-cigarettes or other nicotine replacement products. A Cotinine reading below 15ng/ml signifies a non-user of tobacco or nicotine products. Salivary anabasine (<0.1ng/ml) can be used to confirm if a participant using NRT/ e-cigarettes has also obtained nicotine from tobacco. This will allow us to verify self-reported smoking status of those who have abstained from all nicotine, those using only NRT/e-cigarettes and those still smoking tobacco.

6.11.1. Schedule of Events

Procedures	Screening	Baseline (Part 1)	Baseline (Part 2)	Day 7* (+3 days)	Day 21$ NRT arm only (+/- 2 days)	Day 28 (+5 days)	6 months	12 months
Informed consent	X							
BPE (if not done in previous 3 months)	X							
Eligibility assessment	X							
Randomisation		X						
Demographics			X					
Medical / Smoking history (# self-reported smoking status, including type and amount)			X				#	#
Number of teeth (this can be taken from recent BPE)			X				X	
Expired air Carbon Monoxide							X	X
Fagerstrom Test for Nicotine Dependence (FTND)			X				X	
Mood and Physical Symptoms Scale (MPSS)			X				X	
Oral Health Quality of Life Assessment (OHQoL-UK)			X				X	
Health service utilisation questionnaire			X				X	
AEs and SAEs will be recorded						X	X	X
Concomitant medications (used for AEs)						X	X	X
Ordering of trial products			X*		X$			
Confirmation of receipt of trial products				X*		X$		

Procedures	Screening	Baseline (Part 1)	Baseline (Part 2)	Day 7* (+3 days)	Day 21$ NRT arm only (+/- 2 days)	Day 28 (+5 days)	6 months	12 months
The following assessments are for the Periodontitis subgroup ONLY – collected by the regional blinded hub assessors.								
PPD (Pocket Probing Depths			**X**				**X**	
GI (Gingival Index [Lobene Modified Gingival Index]			**X**				**X**	
PI (Plaque Index [Silness and Loe plaque index])			**X**				**X**	
Gingival recession (used to calculate CAL outcome measure)			**X**				**X**	
BOP (Bleeding on Probing)			**X**				**X**	
CODS- Clinical Oral Dryness Score			**X**				**X**	
Contingent valuation study							**X**	
Collection of periodontal therapy details (7.16)							**X**	
Periodontitis subgroup – Biological Sample collection								
Sub gingival dental plaque			**X**				**X**	
Buccal brush biopsy			**X**				**X**	
Unstimulated saliva (exploratory data collection in selected sites only)			**X**				**X**	
Calculus sample (exploratory data collection in selected sites only)			**X**				**X**	
*= if randomised to NRT or EC $=If randomised to NRT arm only								

6.11.2. Timings of Trial Visits

Routine visits

6 months: In keeping with the pragmatic nature of this trial this follow-up visit will be scheduled around the usual 6 monthly recall visit (that would be recommended for someone with a risk factor such as tobacco smoking). Ideally this should fall 6 months from the baseline visit, but no specific visit timing parameters will be defined.

12 months: As with the 6 month visit this visit will be pragmatically arranged around normal recall periods. However, ideally this visit should be 12 months from baseline, but no specific visit timing parameters will be defined.

Periodontitis subgroup (visits by the blinded hub research team to collect oral health outcome measures)

Baseline: before (maximum of 28 days prior) or on the day of delivery of the intervention.

6 months: on the same day or after (maximum of 28 days after) the 6-month follow-up visit conducted by the primary care team.

6.12. Examiner alignment (periodontitis outcomes)

6.12.1. Hub examiners and research dental nurses

Sessions will be held for the examiners (dentist, dental therapist or dental hygienist) and dental nurses from each hub. This will be held before the first patient recruitment. It will be held as an in-person training event in the Newcastle Dental Clinical Facility. If coronavirus restrictions do not allow this an online version will be provided. The content will include familiarisation with the trial design, database, CRFs, trial processes and trouble shooting. A range of examiner alignment activities will be undertaken as detailed below. Repeatability, reproducibility and Intra-Class Correlation will be assessed for the mean value of the outcome measure (per mouth), to ensure the reliability of the inputs to the statistical models for the final analyses. Percentage of agreement within X units will be assessed for individual site measures, to inform the need for extra training of examiners. The reliability analyses will be performed using variance components random effects models. If new examiners join the study they will be required to complete the examiner alignment exercise individually.

Outcome measure	PPDs and CAL
Training	Discussion of technique via seminar and slides. To include discussion on positioning, pressure and angulation. Pressure gauges/scales will be used to training examiners on probing pressure. Frasaco models will be used to practically implement the skills discussed.
Inter-examiner agreement	1. Pressure gauges/scales will be used to align probing pressure 2. Frasaco models will be used to align PPD/CAL
Intra-examiner agreement	1. Pressure gauges/scales will be used to align probing pressure 2. Frasaco models will be used to align PPD/CAL

Statistics	Inter- and Intra Class Correlation Coefficient (ICC) and percentage agreement within 1, 2, 3 mm

Outcome measure	Gingival Index
Training	Discussion of technique via seminar and slides of example cases.
Inter-examiner agreement	Grading of standardised clinical images
Intra-examiner agreement	Grading of standardised clinical images
Statistics	Inter- and Intra Class Correlation Coefficient (ICC) and percentage of agreement

Outcome measure	Plaque Index
Training	Discussion of technique via seminar and slides of example cases.
Inter-examiner agreement	Grading of standardised clinical images
Intra-examiner agreement	Grading of standardised clinical images
Notes	Score 1 is unable to be calibrated as it involves the physical sweep of the probe to detect plaque which is unable to be recreated for calibration. Scores 0, 2, 3 will be included.
Statistics	Inter- and Intra Class Correlation Coefficient (ICC) and percentage of agreement

Outcome measure	BOP
Training	Discussion of technique via seminar and slides of example cases.
Inter-examiner agreement	Not applicable

Intra-examiner agreement	Not applicable

Outcome measure	CODS
Training	Discussion of technique via seminar and slides of example cases.
Inter-examiner agreement	Grading of standardised clinical images with written descriptions where needed
Intra-examiner agreement	Grading of standardised clinical images with written descriptions where needed
Statistics	Inter- and Intra Class Correlation Coefficient (ICC) and percentage of agreement

Outcome measure	PISA/PESA
Training	Discussion of technique via seminar and example calculations.
Inter-examiner agreement	Calculation of PISA/PESA from set of PPD and BOP indices
Intra-examiner agreement	Calculation of PISA/PESA from set of PPD and BOP indices
Statistics	Do not need to be calibrated for because they are based on PPD/BOP, already covered above.

6.13. Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason within the Case Report Form and participant's medical notes.

The PI may discontinue a participant from the trial at any time if the PI considers it necessary for any reason including:

- Participant withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- An adverse event that requires discontinuation of the trial medication or renders the participant unable to continue in the trial

- Termination of the clinical trial by the sponsor

Participants who withdraw from the trial will not be replaced.

6.14. Storage and Analysis of Samples

It is the responsibility of the trial hub staff to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the applicable legislation (e.g. Global Data Protection Regulation (GDPR)). Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and 2006 Human Tissue (Scotland) Act.

6.15. End of Trial

The end of the trial is defined as the last 12 month follow up visit of the last patient recruited to the trial (LPLV) or the date of the last data collected from the sample analysis, whichever is later.

7. TRIAL INTERVENTIONS

7.11. Oral health advice

All participants will be provided a package of oral health advice, which is usual care in general dental practice. Dental professionals delivering the intervention in ENHANCE-D will utilise existing resources[44] to guide discussion through the topics of oral hygiene, fluoride, diet, alcohol and smoking. The smoking aspect of this package of advice will vary depending on the randomisation group (VBA, NRT or EC).

7.12. Control (Very Brief Advice, VBA)

VBA is usual care for smokers in dental settings. A range of guidance documents recommend VBA, usually following the 3As: Ask, Advise, Act technique. This intervention will be signposting participants to a GP, pharmacy or stop smoking service (SSS). Formal referral can also be completed to SSS, where available. As this is a pragmatic trial, dental professionals will be asked to follow their usual practice in this regard.

Participants in the control group will be free to use NRT or ECs as they wish but these will not be provided by the dental professional providing the advice, nor specifically recommended. It would be impractical and unethical to prohibit NRT or EC use given their availability and because the GP or specialist stop smoking service might recommend or provide these as part of usual care. NRT and EC use will be recorded at follow up for all participants.

7.13. Nicotine Replacement Therapy (NRT)

Participants randomised to the NRT arm will be offered standard NRT. A trained dental professional will provide a single-visit behavioural support intervention (see 7.15) including the offer of NRT. Arrangements will be made for supply of a 12-week course of combination NRT (patch plus faster acting form such as chewing gum or lozenge), in line with current recommendations. Stocks of NRT will be kept centrally at Newcastle Specials Pharmacy and not at each site. Each site will have

demonstration versions of each product and the dental professional will select the most appropriate products and strengths in consultation with the participant. These will be ordered, prepared by the Newcastle Specials Pharmacy and dispatched to the participant's home via secure next day delivery or local dental practice for collection. Initially a 4-week supply will be provided. During the third week the dental professional will either contact them via telephone or SMS text message to check on their status and if required (i.e. they have quit or are still attempting to quit and need more supplies) they will order the further 8 weeks' supply of NRT, to be delivered to the patient's home.

7.14. E-cigarette (EC) starter kit

Participants randomised to this group will be offered an EC starter kit. They will receive the same behavioural intervention (see **7.15**) as the NRT group. As for the NRT group the EC starter kits will be stored centrally and shipped to the patient's home address or local dental practice for collection. The starter kit will include nine 10ml bottles of e-liquid with a choice of one of four packages of flavour and nicotine concentrations. Each site will have demonstration models for training purposes. Participants will be expected to source their own supply of e-liquid after the initial supply and advice will be given as to where to source suitable MHRA registered products.

7.15. Single-visit smoking cessation behavioural intervention

Participants in the NRT and EC arm will be provided with a single-visit behavioural support intervention. Existing evidence suggests that pharmacological interventions (such as the NRT or EC in this proposal) are more effective when delivered alongside behavioural support. Stop smoking specialists are trained in delivering evidence-based behaviour change techniques (BCTs) as part of intensive weekly behavioural support. However, intensive behavioural interventions, such as weekly support, would be unrealistic in busy NHS primary care dental settings. Additionally, the evidence suggests that the dose-response curve is shallow for behavioural support when combined with pharmacotherapy i.e. less intensive interventions are not greatly inferior to more intensive ones. Hence, in keeping with the pragmatic design of this trial we have chosen to use a single-visit behavioural smoking cessation intervention. This intervention will use the most evidence-based, and appropriate of the BCTs used in a traditional intensive weekly behavioural support service. Our single-visit intervention will include the following 5 BCTs:

BCT	How delivered?
Assessing current and past smoking behaviour	Confirm current and past smoking behaviour by discussion with participant. This information is likely to already be know from the medical history but should be revisited.
Providing information on consequences of smoking and smoking cessation	Will inform participants that smoking can lead to: - Tooth staining - Gum disease - Tooth loss - In severe cases, mouth cancer Stopping smoking and help reduce the chances of these or make dental treatments work better

Assessing current readiness and ability to quit	Explore readiness to quit by discussion.
Facilitating goal setting	Set goals such as a quit plan or cutting down to quit (while using NRT/EC)
Offering appropriate written materials	The Cancer Research UK 'You can be Smoke Free' leaflet will be provided. Available at: https://publications.cancerresearchuk.org/publication/you-can-be-smoke-free Any local smoking cessation leaflets as per usual care. Medication package inserts will be included with the NRT or EC as appropriate.

7.16. Periodontal therapy

For those patients with periodontitis, usual periodontal therapy will be provided by the regular dental team. At the 6 month follow-up we will collect information on the details of the care provided as detailed in the dental notes. Specifically,

- Type of instruments used: manual only, powered only, manual and powered
- Local anaesthetic use: yes, no
- Number and duration of appointments
- Staff who delivered the care: dental hygienist, dental therapist or dentist

N.B. We will not be collecting information on 'step 1' periodontal therapy as this will be delivered to all participants in the trial as part of the oral health advice intervention.

7.17. Staff training

Primary dental care GDPs, DTs and DHs

At the seven hubs we will hold training, delivered by: R Holliday, F Ellwood, P Blaylock and a member of the CTU team (or suitable replacements if team member not available). These hub training sessions will be recorded and available as a resource for remote training of individuals unable to make the training or joining the trial later.

This will cover three main topics:

- Trial processes
- GCP
- Intervention training

In keeping with the pragmatic nature of this trial, the majority of the training for the intervention will use existing and well-established online training packages. This training will be provided through the National Centre for Smoking Cessation and Training (NCSCT) (www.ncsct.co.uk) who will provide reports on course access/completion. Dental professionals will complete 4 courses:

- VBA on Smoking
- Stop Smoking Practitioner Training and Assessment Programme. This provides training on all the core competencies (knowledge and skills) for helping people stop smoking. This is a generic course (relevant to health professionals supporting any patient group/members of the public). The course is followed by an assessment of core knowledge and practice skills and upon successful completion a certificate is awarded.
- Stop Smoking Medications (more detail on NRT)
- E-cigarettes: A guide for healthcare professionals

At the hub training session there will be a session focusing on adapting the standard NCSCT training into a single-visit intervention and incorporating this into the oral health advice package.

Each site will identify two dental professionals who will receive training on the interventions. This will vary by practice but could be the lead dentist, DT, DH or other members including the DN. Dental professionals will be reimbursed for 4 days of their time to complete the NCSCT courses and hub/GCP training.

8. TRIAL MEDICATIONS - NRT

8.1. Name and Description of IMP

For the purpose of this trial Nicotine Replacement Therapy (NRT) products listed in section 8.4 below will be classed as the IMP.

8.2. Drug Storage and Supply

The Reference Safety Information (RSI) for NRT is located in section 4.8 of the NRT Summary of Product Characteristics (SmPC) for each product. A record of which version of the SmPC constitutes the current approved RSI will be kept in the Trial Master File.

The IMP will be stored at a central pharmacy (Newcastle Specials) and dispensed directly to participants by recorded delivery.

The trained research team member (DN, DH, DT or dentist) will deliver the smoking cessation interventions and supply the NRT (by ordering from the central pharmacy). NRT, in any form currently available in the UK, is classified as a General Sales List (GSL) medicine. There are no legal restrictions on who can supply or administer a GSL medication[45]. Providers will follow a

simple protocol for the provision/order of NRT.

8.3. Preparation and Labelling of IMP

This trial has been risk assessed as Type A in line with the MHRA Risk Adaptive Process - no higher than the risk of standard medical care. The use of these products is classed as standard of care within clinical practice and therefore pose no greater potential risk than that of standard medical care. There will therefore be no requirement for accountability, segregated storage, temperature monitoring or labelling compliant with annex 13 performed for this trial.

8.4. Dosage Schedule & Modifications

Nicotine Replacement Products	***Notes***
Patches NiQuitin 7 mg, 14 mg, 21 mg *[24-hour patch]* 24-hour patch is recommended if a patient experiences strong cigarette cravings upon waking	Applied once a day, at the same time each day and preferably soon after waking, to a different non-hairy, clean, dry skin site and worn continuously for 24 hours NiQuitin therapy should usually begin with NiQuitin 21 mg and be reduced according to the following dosing schedule: NiQuitin 21 mg (first 6 weeks) NiQuitin 14 mg (next 3 weeks) NiQuitin 7 mg (final 3 weeks) Light smokers (e.g. those who smoke less than 10 cigarettes per day) are recommended to start at Step 2 (14 mg) for 6 weeks and decrease the dose to NiQuitin 7 mg for the next 6 weeks.
Nicorette invisi 10 mg, 15 mg, 25 mg *[16-hour patch]* Is a patient does not experience strong cigarette cravings upon waking, 16-hour patch is recommended	Intended that the patch is worn through the waking hours (approximately 16 hours) being applied on waking and removed at bedtime. For best results, most smokers are recommended to start on 25 mg / 16 hours patch (Step 1) and use one patch daily for 8 weeks. Gradual weaning from the patch should then be initiated. One 15 mg/16 hours patch (Step 2) should be used daily for 2 weeks followed by one 10 mg/16 hours patch (Step 3) daily for 2 weeks Lighter smokers (i.e. those who smoke less than 10 cigarettes per day) are recommended to start at Step 2 (15 mg) for 8 weeks and decrease the dose to 10 mg for the final 4 weeks
Gum Nicorette gum 2 mg, 4 mg *[2 flavour options: freshmint or fruit]*	The strength of gum to be used will depend on the smoking habits of the individual. In general, if the patient smokes 20 or less cigarettes a day, 2 mg nicotine gum is indicated. If more than 20 cigarettes per day are smoked, 4 mg nicotine gum will be needed Should be used whenever the urge to smoke is felt or to prevent cravings in situations where these are likely to occur. The chewing gums should be used whenever there is an urge to smoke according to the "chew and rest" technique described on the pack. After about 30 minutes of such use, the gum will be exhausted. We will provide 2 packs at initial supply then at week 4 the resupply - *consideration given to the strength needed based on the participants need*s - up to 4

	additional packs can be supplied. A maximum of six packs of gum or lozenge will be provided in total.
Lozenges Nicorette lozenge 2 mg, 4 mg *[2 flavour options: fruit, mint]*	The strength of lozenge to be used will depend on the smoking habits of the individual. In general, if the patient smokes 20 or less cigarettes a day, 2 mg nicotine lozenge is indicated. If more than 20 cigarettes per day are smoked, 4 mg nicotine lozenge will be needed. Should be used whenever the urge to smoke is felt or to prevent cravings in situations where these are likely to occur. One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved. You should not chew or swallow the lozenge. We will provide 2 packs at initial supply then at week 4 the resupply - *consideration given to the strength needed based on the participants need*s - up to 4 additional packs can be supplied. A maximum of 6 packs of gum or lozenge will be provided in total.

8.5. Known Drug Reactions and Interactions

No clinically relevant interactions between nicotine replacement therapy and other drugs has definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

Healthcare professionals are reminded that smoking cessation itself may require the adjustment of some drug therapy.

For example, when a patient stops smoking*:*

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs. Examples of drugs where increased monitoring would be required includes clozapine, olanzapine, and theophylline.

8.6. Concomitant Medications

None

8.7. Assessment of Compliance

Participants will be asked to report use at their 6 month and 12 month follow-up visits.

9. CONSUMER PRODUCTS

9.1. Name and description

Customised e-cigarette starter kit to include:

- Stainless Steel Aspire PockeX e-cigarette
- Coil replacement pack
- 3-pin plug
- 10 x Halo standard 10ml e-liquids

Choice of four e-liquid bundles:

A (Tobacco focus)	4 x Classic Virginia tobacco 1.8% 3 x Classic Virginia tobacco 1.2% 1 x Menthol Blast 1.8% 1 x Raspberry Crush 1.8% 1 x Manic Mango 1.8%
B (Menthol focus)	4 x Menthol Blast 1.8% 3 x Menthol Blast 1.2% 1 x Raspberry Crush 1.8% 1 x Manic Mango 1.8% 1 x Classic Virginia tobacco 1.8%
C (Full mix)	2 x Menthol Blast 1.8% 1 x Menthol Blast 1.2% 1 x Raspberry Crush 1.8% 1 x Raspberry Crush 1.2% 1 x Manic Mango 1.8% 1 x Manic Mango 1.2% 1 x Classic Virginia tobacco 1.2% 2 x Classic Virginia tobacco 1.8%
D (Non-tobacco mix)	2 x Menthol Blast 1.8% 1 x Menthol Blast 1.2% 2 x Raspberry Crush 1.8% 1 x Raspberry Crush 1.8% 2 x Manic Mango 1.8% 2 x Manic Mango 1.2%

9.2. Storage and Supply

The EC starter kit will be stored at a central pharmacy (Newcastle Specials) and dispensed directly to participants by recorded delivery.

The trained research team member (DN, DH, DT or dentist) will deliver the smoking cessation interventions and supply the EC starter kit (by ordering from the central pharmacy). As a consumer product there are no legal restrictions on who can supply ECs. There is a minimum age of 18 years for the provision of e-cigarettes which matches with our study inclusion criteria. Providers will follow a simple protocol for the provision/order of ECs.

9.3. Known Reactions and Interactions

No clinically relevant interactions between nicotine replacement therapy and other drugs has definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

Healthcare professionals are reminded that smoking cessation itself may require the adjustment of some drug therapy.

For example, when a patient stops smoking*:*

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs. Examples of drugs where increased monitoring would be required includes clozapine, olanzapine, and theophylline.

10. PHARMACOVIGILANCE

10.1. Definitions

Term	Definition
Adverse Event (AE)	One of the pre-specified 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 or 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
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.

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 that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
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 upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

10.2. Recording and Reporting AEs and SAEs

All pre-specified AEs (see section 10.3) whether related to IMP or not, occurring from point of randomisation to end of end of trial participation must be recorded in the eCRF as well as the participant's dental notes.

For AEs we will be recording; severity, seriousness, causality and any concomitant medication used.

Where any of these AEs are serious they must be reported to NCTU on an SAE form and also recorded in the eCRF and flagged as serious.

There will also be the option for participants to report AEs other than the pre-specified AEs listed section 10.3. Where any of these other AEs fit the criteria for serious, they should be reported to NCTU by the research staff on an SAE form.

Following the defined monitoring period for SAEs, investigators are still required to report any SARs they become aware of.

All SAEs/SARs must be reported to NCTU on an SAE Form via **nctu.enhanced.sae@nhs.net** within 24 hours of research staff becoming aware of the event.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24 hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description

- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Severity
- Causality (to the intervention they were randomised to) in the opinion of the investigator
- Whether the event is considered expected or unexpected in accordance with the approved

Reference Safety Information if a causal relationship is suspected

Any change of condition or other follow-up information should be submitted to the NCTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

10.2.1. Exclusions from expedited reporting

Any events other than those pre-specified in section 10.3 where any relationship to trial participation is unlikely does not need to be reported on an SAE form.

10.3. Pre-specified AEs

As part of the trial, a number of adverse events of interest relating to e-cigarettes will be collected as part of routine data collection. The events listed below are considered to be adverse events of interest and will therefore be collected. There will also be the option for participants to report other adverse events.

- Shortness of breath
- Cough
- Phlegm
- Nausea
- Throat/Mouth Irritation (including mouth ulcers, abscesses)
- Sleep Disturbance
- Headache
- Mouth dryness
- Dizziness/ Feeling Faint

10.4. Recording and Reporting SUSARs

All SUSARs occurring from first administration of IMP until the end of the trial must be reported to the MHRA and REC. The Sponsor will perform this reporting.

The assessment of expectedness will be performed by the CI on behalf of sponsor against the approved Reference Safety Information (RSI) for the trial. The RSI is contained within section 4.8 of the appropriate Summary of Product Characteristics for each NRT product. .

Fatal and life-threatening SUSARS must be reported no later than 7 calendar days after the [sponsor/CI/NCTU] has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported no later than 15 calendar days after the [sponsor/CI/NCTU] has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

The reporting timeframe starts at day 0 when the [Sponsor/CI/NCTU] is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Patient trial number and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

To ensure adherence with the required reporting timeframes, sites must notify NCTU of SARs immediately but no later than 24 hours after becoming aware as outlined in section 10.2 above. The site is expected to fully cooperate with the [Sponsor/CI/NCTU] in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

PIs will be informed of all SUSARs by the [Sponsor/CI/NCTU].

10.5. Responsibilities

Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using clinical judgement in assigning seriousness and causality
- Ensuring that all SAEs and SARs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator(s)

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using clinical judgement in assigning seriousness and causality of SAEs where it has not been possible to obtain local medical assessment.
- Using approved Reference Safety Information (RSI) to assess expectedness for SARs on behalf of sponsor.
- Reviewing RSI at least annually and confirming of any changes are required.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs.
- Preparing the clinical sections and final sign off of the DSUR.

Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- Assessment of expectedness for any SARs(may be delegated to the CI)
- Expedited reporting of SUSARs to the CA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs. (may be delegated to NCTU.
- Reviewing RSI at least annually (may be delegated to NCTU)
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC. (may be delegated to NCTU)

TSC/DMC

- *Review of safety data collected to date to identify any trends*

10.6. Notification of Deaths

Any deaths during the trial will be recorded in the trial database.

10.7. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the [Sponsor/CI/NCTU] must be notified immediately and details of the USM given. The [Sponsor/CI/NCTU] must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the [Sponsor's/NCTU's] standard operating procedures.

10.8. Development Safety Update Reports

Data relating to SAEs will also be provided to the regulatory authorities in the annual Development Safety Update Report (DSUR). DSURs must be submitted annually until submission of the End of Trial notification. The date of the Data Lock Point (DLP) for the annual reporting period is the date of the anniversary of the CTA.

The DSUR must be submitted to the MHRA no later than 60 calendar days after the DLP.

The Trial Manager is responsible for keeping track of when the DLP is due and to notify the TMG of the impending date. Following the DLP, the SAR line listings and cumulative summary tabulation of SAEs should be prepared. Prior to the DLP the Trial Manager should ensure that the RSI is reviewed by the CI to determine if any change is required for the forthcoming reporting period. If a change is required a substantial amendment will need to be submitted and approved prior to the start of the new reporting period (begins the day after DLP) in order for the new RSI to be used.

DSURs must be reviewed by the relevant members of the TMG including sponsor and the outcome of the review documented within the TMG minutes. The draft DSUR should also be submitted to the NCTU Quality Assurance Team for review.

For CTIMP trials which are classified as type A and have been approved under the notification scheme, a simpler and shorter form may be submitted in lieu of a full DSUR. The short format DSUR must be submitted on the Health Research Authority (HRA) CTIMP Annual Progress Report form. On submission of the annual report, the cover letter should indicate that it is an Annual Progress Report (APR) in lieu of a full DSUR and include the EudraCT number and CTA reference number.

Once the DSUR has been agreed by all parties, within the 60 calendar day timeline, it must be submitted to the MHRA and REC that gave a favourable ethical opinion for the trial.

11. RISK ASSESSMENT

This trial is categorised as:

Type A = no higher than the risk of standard clinical care

N.B. We have already shared a draft protocol with the MHRA who confirmed type A status.

12. STATISTICAL CONSIDERATIONS

12.1. Analysis Population

Analysis populations are defined as follows:
Intention to treat (ITT): all randomised participants in the groups to which they were randomised.

Safety population: all randomised participants who accepted the offer of study intervention. The analyses will be performed according to the intervention participants were randomised to, and also according to participants' self-reported usage.

12.2. Statistical Analyses

The analysis of all outcome measures will be described in detail in a pre-specified Statistical Analysis Plan (SAP) that will be reviewed by the trial's oversight committees and signed off by the co-CIs prior to any comparative analyses being undertaken.

We propose to test the superiority of either EC or NRT compared to VBA for the primary outcome and the key secondary outcome, according to Bonferroni based gate-keeping method [46]. For each outcome, if at least one of the two hypothesis tests for EC or NRT compared to VBA is rejected we will test the superiority of EC compared to NRT for that outcome. The gatekeeping method allows us to complete several comparisons across both important outcomes by splitting and carrying forward 'unused' alpha. Figure 1 provides a simplified description of this technique.

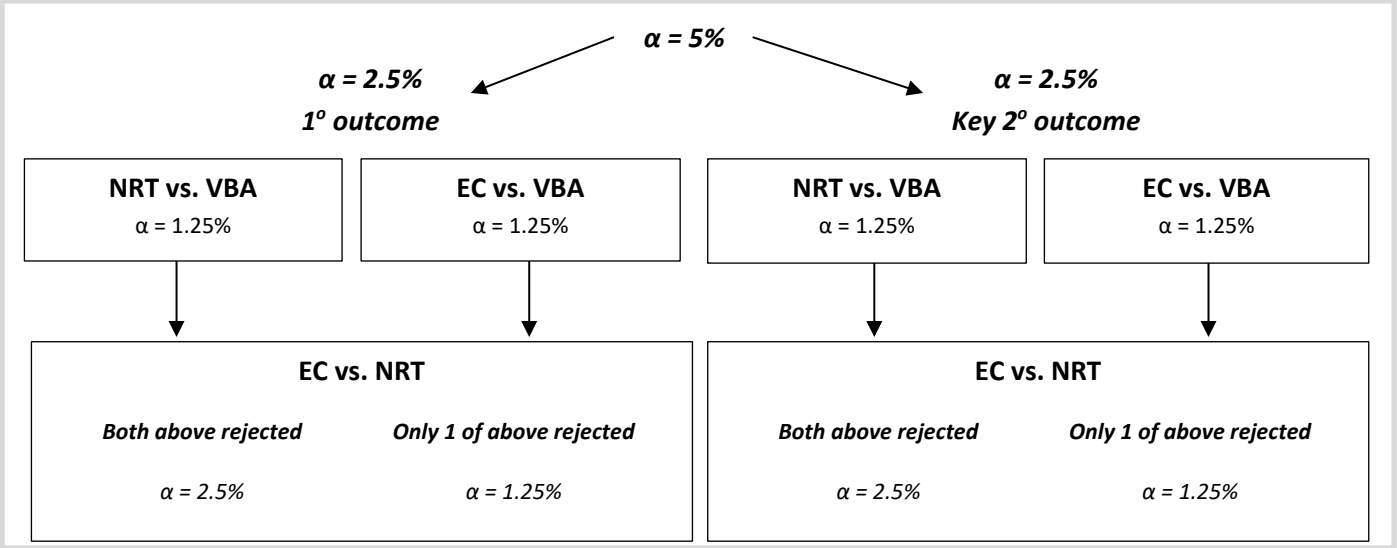

Figure 1. Bonferroni-based gatekeeping method.

12.2.1. Analysis of the Primary Outcome

The primary outcome of biochemically verified smoking abstinence at 6 months (all participants) will be analysed using mixed-effects logistic regression adjusted for the stratification factors, hub (random effect) and baseline periodontal status (fixed effect). Any participants with missing data (of any type) will be regarded as still smoking and therefore all participants will have smoking abstinence data. To test the null hypothesis of no treatment difference we will firstly compare EC to VBA and NRT to VBA, followed by a comparison of EC to NRT according to the decision criteria detailed in Figure 1. Results will be presented as odds ratios with P-values extracted directly from the model. Statistical significance will be at the level determined by the Bonferroni-based gate-keeping method. All comparisons will also be presented with 95% confidence intervals[47].

Sensitivity analyses will be conducted around the assumption that if abstinence is not confirmed the participant is still smoking - these will be pre-specified in the SAP.

12.2.2. Secondary Outcome measures

12.2.2.1. The key secondary outcome measure (periodontitis subgroup)

The key secondary outcome of percentage of sites at 6 months with PPD≥5mm (in the periodontitis subgroup) will be analysed using a linear mixed-effects model adjusted as for the primary outcome and for baseline percentage of sites with PPD≥ 5mm. Results will be presented as odds ratios with P-values extracted directly from the model. Statistical significance will be at the level determined by the Bonferroni-based gate-keeping method. All comparisons will also be presented with 95% confidence intervals [47].

Analyses will be conducted for available data according to the ITT principle. Missing data mechanisms will be considered and sensitivity analyses may be carried out on an imputed dataset - these will be pre-specified in the SAP.

12.2.2.2. All other secondary outcome measures

Analyses will follow the same approach as that described for the primary outcome measure (with the addition of adjusting for baseline where the outcome is measured at baseline). The binary secondary outcome measures, such as continuous biochemically verified smoking abstinence at 12 month, will be analysed using a mixed-effects logistic regression model. Categorical secondary outcomes, such as Fagerstrom Test for Nicotine Dependence, will be analysed using a multinomial mixed-effects regression model. Count secondary outcomes, such as number of teeth, will be analysed using a mixed-effects Poisson regression model. Continuous secondary outcome measures, such as Oral Health Quality of Life Assessment score, will be analysed using a linear mixed-effects regression model. Results will be presented with associated 95% confidence intervals.

12.3. Sample Size Calculations

Primary outcome (biochemically verified smoking abstinence at 6 months): assuming a rate for VBA of 6% [9] with a minimal clinically important difference (MCID) of 7% [19, 48], 85% power and type 1 error rate of 1.25%, a total of 1460 participants (VBA= 292; NRT/EC = 584) would be required to perform a one-sided test for each hypothesis (NRT vs VBA, EC vs VBA). If both null hypotheses are rejected we will carry forward a type I error rate of 2.5% and based on a NRT rate of 11% we can detect a difference of 7% with 93% power and 6% with 84% power (one-sided test EC vs NRT). If only one null hypothesis is rejected we will carry forward a type I error rate of 1.25% with which we can detect a difference of 7% with 88% power. Note that this is not inflated for attrition in line with standard research practice in this field [27].

Key secondary outcome (percentage of periodontal sites at 6 months with PPD ≥5 mm for patients with periodontitis): assuming a target absolute mean difference of 4.75% (a 25% relative reduction) [49], a SD of 10.1% [50], 80% power and type 1 error rate of 1.25%, 15% attrition, a total of 455 participants (VBA= 91; NRT/EC = 182) would be required to perform a two-sided test for each hypothesis (NRT vs VBA, EC vs VBA). This test has been powered using the estimated standard deviation derived from an analysis of covariance, given the analysis will adjust for baseline percentage of sites with PPD≥ 5mm [51]. If both null hypotheses are rejected we will carry forward a type I error rate of 2.5% with which we can detect a mean difference of 4.75% (a 25% relative reduction) [49] with 97% power (two-sided test EC vs NRT) and 3.8% (a 20% relative reduction) with 85% power. If only one null hypothesis is rejected we will carry forward a type I error rate of 1.25% and we can detect a mean difference of 4.75% with 95% power (two-sided test EC vs NRT).

The sample size calculations were performed in SAS version 9.4 of the SAS System for Windows 7, copyright © 2012 SAS Institute Inc.; the smoking cessation sample size using proc power twosamplefreq test=pchi, and the PPD sample size using proc power twosamplemeans. Both sample sizes were verified in Stata 16[52] using power twoproportions test(chi2) and power twomeans respectively.

13. STUDY WITHIN A TRIAL (SWAT)

As part of The James Lind Alliance Priority Setting Partnership: PRioRiTY I & II studies the top ten most important questions in trial recruitment and retention were identified. [53, 54]A key focus is how trials can be designed to minimise staff burden and what the barriers and enablers to participation in randomised trials for clinicians/ healthcare professionals are. Within primary care dental research the dentist has almost always been the 'PI' or 'lead'. Although the dentist is the lead in a dental team, they are also the most expensive and often the busiest. There is considerable scope for other members of the dental team (namely DT or DH) to act as the PI, where the trial is within their scope of practice. The ENHANCE-D Trial is within the scope of DT/DH and hence our SWAT will uniquely give each practice the chance to have a DT or DH as the 'PI' (they can still be supported by a dentist in their team). This means we may have DT or DH taking consent, confirming eligibility and assessing AEs. Non-medical PIs have been used before in similar studies, such as the recent NIHR-funded ECstudy[19], and we will obtain the necessary MHRA authorisations during the approvals process. Our hypothesis is that these other members of the dental team may have higher motivation and less competing time pressures, such as running a business, leading to more efficient delivery of the trial at the site level. This SWAT will be non-randomised as not all practices have a DT/DH who could take on this role. Hence practices will self-select into either dentist or DT/DH lead sites. Although SWATs are mostly randomised in design, this is not practical in our setting, and similar approaches have been used in existing SWATs[55]. Recruitment rates, retention rates and process factors will be evaluated. Qualitative research will attempt to explain any differences observed.

14. HEALTH ECONOMICS

The health economic component will include an economic evaluation in the form of a cost-effectiveness analysis (CEA) and a cost-benefit analysis (CBA). The economic evaluation will be conducted according to best practice guidelines[56].

The CEA will be using the trial primary outcome (smoking abstinence) as the outcome measure. Alongside the CEA, a cost-benefit analysis (CBA) will also be conducted using a measure of willingness-to-pay (WTP) for the interventions and primary outcome (smoking abstinence at 6 months). A CBA approach offers additional added value to the CEA as measures of WTP can capture a broader range of benefits and may be better suited to the measurement of impact from this trial. WTP values for the CBA will be elicited via a contingent valuation study (CVS), in which preferences for each intervention and the primary outcome are obtained. The CBA will be administered at six-months via an online survey. It is likely this survey will take the form of a shuffle payment card [57]. The values used in the CVS will be informed by the relevant literature, trial team and PPI representatives. Data will be collected within the trial and will be used to calculate costs and estimate outcomes for the CEA. The interventions will be micro-costed and bespoke participant questionnaires (healthcare utilisation) and eCRF will capture data on medications (only medications related to smoking cessation and managing any symptoms associated with smoking cessation will be considered), dental service use and other subsequent healthcare service use. Participant questionnaires, created using input from the PPI representatives, will be administered at baseline and 6 months post-randomisation to capture service use throughout the follow-up time period. Unit costs for these services will be obtained from routine

data sources and trial specific estimates[58]. The analysis will be conducted from an NHS and personal/social services perspective. Unit costs will be combined with service use to estimate costs per participant in each arm of the trial. Mean costs per intervention arm can then be calculated. Sensitivity analyses will estimate the costs incurred by participants in the trial. Participant costs will be collected as part of the participant questionnaires.

For the CEA, the results will be presented as point estimates of mean incremental costs and effects. Regression analysis (using seemingly unrelated regression) will be applied to costs and effects to estimate adjusted point estimates of incremental costs, effects and cost-effectiveness[59]. Stochastic analyses (plots of cost and effects and cost-effectiveness acceptability curves) using bootstrapping techniques will also be conducted to explore uncertainty in the estimate of cost-effectiveness[60-62]. The results of the CBA will be presented as incremental costs and effects (effectiveness will be estimated by the mean WTP for smoking cessation multiplied by the primary outcome) and incremental net benefits, where net benefits = incremental effects – incremental costs. The results of the CBA will also be used to estimate the net benefits of each intervention which will be determined by mean WTP of the intervention – mean costs of the intervention.

For the economic evaluation (CEA and CBA) deterministic sensitivity analyses will be performed to explore key uncertainties e.g. valuations of time away from usual activities, sub-groups, etc. Where appropriate, these analyses will be combined with a stochastic analysis with the results presented in the same ways as described above. Furthermore, missing data is expected from the trial; methods of imputation to address missing data will be determined once the full dataset is available and missing data has been identified and characterised.

Both the CEA and CBA will include an assessment of the distribution of outcomes according to socioeconomic status in order to explore any possible impacts of the intervention on inequalities.

An analysis of the periodontitis subgroup will use the same methods as described above for the CEA. This analysis will be largely exploratory as it is expected that the sub-group sample size will be insufficient for robust conclusions to be drawn on cost-effectiveness.

15. QUALITATIVE EVALUATION

A qualitative evaluation will explore participants' experiences from a range of stakeholder perspectives that have the potential to influence adoption of the proposed interventions in NHS primary dental care. This qualitative component of the larger RCT is not a process evaluation but will be based upon Normalisation Process Theory[63] (NPT) which will act to guide and inform our analytic interpretation of the findings with respect to potential implementation and integration in NHS primary dental care settings. Normalisation Process Theory is typically described as a 'middle-range theory' that can inform implementation research and may provide structure to inform coding and analysis under the four constructs of: Coherence; Cognitive Participation; Collective Action and Reflexive Monitoring[64].

Patients' perceptions of the EC and NRT interventions compared to usual care (VBA) will be sought, alongside dental professionals' perspectives of facilitators and barriers to provision of these interventions within the NHS. A third participant group will comprise NHS commissioners and service managers who hold the responsibility for securing appropriate local dental services. Collectively, the

qualitative data will provide valuable insight, contributing to our knowledge on intervention acceptability, implementation issues as well as regulatory and NHS service considerations. Socioeconomic barriers/facilitators will be explicitly explored to help triangulate the socioeconomic data analyses.

Following favourable NHS ethical review, we anticipate the qualitative component will involve approximately 32 patients, 16 dental professionals and 5 NHS commissioners/ service managers, although data saturation will determine the actual participant recruitment numbers involved. The indicative number of participants is based upon purposive maximum variation sampling, including the variables of sex, age, UK region, the dental practice at which the intervention was delivered and patients from all trial arms. For dental professionals, the sample will seek to include dentists, dental therapists (DT), dental hygienists (DH) and dental nurses (DN) who may all be involved in delivering different aspects of the trial interventions within NHS primary dental care and working under different NHS dental contractual regulations. Written consent for this element of the wider trial will be sought at an early stage and interested participants will be selected by the research team, based upon their fulfilment of one or more of the variables listed. Diversity within the sample will be limited only by the number of participants who provide written informed consent to participate in the qualitative component of the wider trial.

Using the above sampling strategy, selected participants recruited to the main RCT will be invited to take part in the qualitative component at two time points within the trial: at approximately 1 month following initial receipt of their allocated intervention and after their 6-month appointment. Selected participants for the qualitative study will be invited to participate in both the 1-month and 6-month time points, however, should consent only be obtained for one time point, that data would still be analysed and further participants invited as necessary in order to achieve data saturation. Dental professionals will be invited to participate on the same basis as patients, but NHS commissioners/ service managers will only be interviewed once at approximately 9-12 months following the start of patient recruitment in the wider trial.

Qualitative methods will comprise a choice of face-to-face (present-in-person) or online semi-structured interviews, telephone interviews or focus groups. To maximise response and to reduce the burden upon participants, selected respondents who have provided written informed consent and who meet the sampling criteria will be offered their preferred format. All interviews (face-to-face, online or telephone) and focus groups will be audio-recorded following an agreed topic guide before being transcribed verbatim by a professional transcription company and analysed thematically. Initial topic guides will be constructed (one per participant group) based upon the previous experiences of the research team, but they will be revised as necessary during the data collection process.

Interviews and focus groups will be led and analysed initially by an experienced qualitative researcher (research associate) supported by R Holmes and E McColl. Emergent themes will be discussed regularly by the qualitative research team to inform development of the topic guide and to achieve consensus for coding and analysis. Coding will be checked in 10% of transcripts by one of the qualitative research team (R Holmes). Qualitative data (transcripts) will be imported into NVivo software to facilitate management and secure storage on password-protected Newcastle University servers accessible only by the qualitative research team. The research team will follow ‘Standards for reporting qualitative research: a synthesis of recommendations’ (SRQR)[65].

16. DATA HANDLING

The Clinical Data Management System (CDMS) used for the electronic case report forms (eCRFs) in this trial is fully compliant with all regulatory frameworks for research of this nature. The CDMS is Red Pill supplied by Sealed Envelope™, in summary:

- Has an inbuilt daily back up facility, stored redundantly at two sites, which is encrypted.
- Uses a secure web-based interface for data entry, no data is stored at computers at site.
- Users are assigned role-based permissions specific to their site and study role.

For this trial, trial data will be collected by the PI and their delegated nominees and recorded in the relevant e-CRFs. Patient identification on the e-CRF will be through a unique participant ID, allocated at screening. These IDs will specify hub, site and individual patient and will be provided sequentially at each site. A Patient Identification Log will be held within the ISF stored in a locked office at site, which will link the patient's name to the participant ID and will allow identification at site. Patients cannot be identified from e-CRFs.

Participants will be completing questionnaires for this trial on paper forms at baseline and 6 months. These answers will be transcribed by the site staff on to the Red Pill database and the paper originals will remain at site for future monitoring review.

16.1. Data Handling and Record Keeping

Overall responsibility for data collection lies with the Chief Investigator. Data will be handled, computerised and stored in accordance with the General Data Protection Regulations 2018. Paper copies of trial-related documentation will be annotated, signed and dated, and filed in the dental records. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

The trial specific Data Management Plan will include details of how the quality of the data will be monitored. Validations will be built into the Red Pill database, whilst additional manual validations will also be made and will be detailed in the Data Validation Plan.

16.2. Data linkage

Informed consent will be obtained for data linkage. This will allow follow up with routine administrative data (primary and secondary care dental and medical health records data) during the trial and over the long term.

16.3. Access to Data

Staff involved in the conduct of the trial, including the PIs, trial management team and NHS staff involved in screening and intervention will have access to the Investigator Site File.

The trial data and participant dental records may be looked at by NCTU during monitoring, the Newcastle upon Tyne Hospitals NHS Foundation Trust during monitoring or auditing and the Medicines and Healthcare products Regulatory Agency (MHRA) during inspection.

Secure pseudoanonymised electronic data may be released to the Trial Statistician for analysis. The PI and trial sites staff involved with this trial may not disclose or use for any purpose other

than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Password limited access to the Red Pill database within Sealed Envelope will be restricted to one's own particular role and will be granted to each site's PI and their delegated data entry personnel at that site/hub. NCTU trial management team will have access to the trial database for monitoring purposes.

16.4. Archiving

All trial data will be stored for 5 years in accordance with UK GCP legislation and the Sponsor and NCTU SOPs.

17. MONITORING, AUDIT & INSPECTION

Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running of the trial and will consist of the CI, members of NCTU, statistician(s) and, as required, other members of the co-applicant team. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. TMG meetings will occur 4-6 weekly. Progress will be monitored proactively according to agreed trial timelines and any issues addressed. The TMG will liaise with the Trial Steering Committee (TSC), providing updates on trial progress and highlighting any issues arising.

Trial Steering Committee (TSC)

The TSC will be established to provide overall –independent oversight of the trial, and will oversee trial conduct and progress. The TSC will consist of an independent chair, together with at least two other independent members, two Patient and Public Involvement (PPI) representatives and the Chief Investigator. The TSC will meet approximately 6 monthly throughout the trial and meetings may be attended by non-voting observers including those from the NCTU, co-applicant team, Sponsor and Funder.

Independent Data Monitoring and Ethics Committee (IDMEC)

The DMC will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The DMC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial. The DMC will meet approximately 6 monthly throughout the trial.

Principal Investigator

Each site will be led by a Principal Investigator who will be responsible for trial conduct. They will be supported by other staff who will all be GCP trained.

The Principal Investigator will be responsible for oversight of the trial conduct at site. The NCTU will provide day-to-day support for the site and training, site initiation visits and routine monitoring visits.

Monitoring

Quality control will be maintained through adherence to Sponsor and NCTU SOPs, trial protocol, GCP principles, research governance and clinical trial regulations.

Monitoring to ensure appropriate trial conduct and data collection will be carried out by the NCTU. Electronic data will be stored in secure, password-protected computers. NCTU staff will use a combination of central monitoring, off-site monitoring and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and the trial protocol.

The following will be monitored:

- Presence, validity and correct completion of completed original consent forms in the Investigator Site File (ISF) and copies in participant's medical records.
- Comparison of original consent forms to the patient identification (enrolment) list.
- Reported serious adverse events, by verification against participant's medical records (source data verification).
- Presence of essential documents in the ISF and trial files
- Endpoint data, including for the primary endpoint, for a percentage of trial participants, by source data verification.
- Applications for trial authorisations and submissions of progress/safety reports, for accuracy and completeness, prior to submission.
- Eligibility data for a percentage of trial participants, by source data verification.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The site PIs and institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data and documents relating to the trial. All data will be retained for 5 years.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1. Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol or urgent safety measures that occur during the trial. The Sponsor will notify the REC of any SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

18.2. Peer Review

This trial is funded by the NIHR HTA and, therefore, has been subject to the NIHR HTA peer review process for funding applications. This includes an external peer review followed by a review by the funding panel members.

18.3. Public and Patient Involvement

Patients have been involved throughout the trial concept and design phase. Funding has been provided for an expert patient representative to be involved on the TMG/TSC to ensure that the trial remains patient centred and to support engagement

18.4. Regulatory Compliance

The trial will be conducted in accordance with the The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 and subsequent amendments and local policy. All parties must abide by these regulations and the ICH GCP guidelines.

NCTU will support the CI in obtaining a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial (see section 10).

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial (see section 6.10).

The CI and NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

18.5. Protocol Compliance

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI will retain overall responsibility.

Protocol deviations, non-compliances and breaches are departures from the approved protocol. Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events should be documented on the deviation tracking log (this will be provided as part of the ISF). NCTU will ask the site to provide copies of their deviation tracking log at intervals throughout the trial and before any monitoring visits. If no deviations have been identified during a particular interval, site are required to send an email to the NCTU to confirm this.

If a deviation constitutes a violation, the site must complete a protocol violation form (a blank template will be provided to the site as part of the ISF) and send a copy of this completed form to the Trial Manager in NCTU within 3 working days. The violation must also be entered on to the deviation tracking log.

Unintentional protocol deviations will be documented and reported to the CI and sponsor. Where necessary, Corrective and Preventative Actions (CAPA) will be implemented. These will also be documented and reported to the CI and sponsor.

Deviations found to frequently recur at a site are not acceptable and could be classified as a serious breach.

18.6. Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The NCTU will notify the MHRA and the NHS REC within the required timelines in accordance with the sponsor and NCTU SOP.

18.7. Data Protection and Patient Confidentiality

Personal data will be regarded as strictly confidential. All data retained at site and sent electronically to the main co-ordinating centre will be sent securely and will contain a unique trial identifier number. The secure password-protected eCRF database will contain date of birth, ethnicity and sex at birth. This is essential for participant identification and verification. This information is also required for SAE reporting via secure email.

Participants NHS numbers (England) or CHI numbers (Scotland) will be collected to allow for long term follow up where consent has been given for this. NHS/CHI numbers will be transferred to the NCTU by secure email (i.e. nhs.net to nhs.net or encrypted email) to nctu.enhanced.conf@nhs.net. As Personal Identifiable Data, participants NHS number will be stored in line with Newcastle University Information Governance for Health Research, including a Safe Haven being set up to store the data and enrolling onto the Newcastle University's Data Security and Protection Toolkit (DSPT). Access to data will be restricted to members of the trial team who require it.

All personnel with access to trial data will be qualified and trained in, and will comply with ICH GCP.

A Participant Identification List will be the only document retained within the ISF, which contains full details of patients' hospital numbers, patient names and unique trial identifier numbers (participant ID).

The trial will comply with the General Data Protection Regulations, 2018. All trial records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access to those who are named on the delegation log.

18.8. Indemnity

The Newcastle Upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts for potential liability in respect of negligent harm arising from the conduct of the trial.

As Sponsor, the Newcastle upon Tyne Hospitals NHS Foundation Trust will provide indemnity in respect of potential liability and negligent harm arising from trial management.

Indemnity in respect of potential liability arising from negligent harm related to trial design is provided by Newcastle University.

This is a non-commercial trial and therefore there are no arrangements for non-negligent compensation.

18.9. Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor the Trial Management Group and Trial Steering Committee.

Substantial amendments will be submitted to the REC, HRA and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by the NCTU.

18.10. Post-Trial Care

Following the completion of the trial, trial participants will revert to clinician led care according to current guidelines.

18.11. Access to the Final Trial Dataset

Until publication of the trial results, access to the full-blinded dataset will be limited to the Trial Management Group and to authors of the publication.

In line with General Data Protection Regulation (GDPR), explicit consent must be obtained via the informed consent form from each trial participant to allow data sharing to occur. In accordance with the NIHR position on the sharing of research data published in May 2019, which is in line with the UK Policy Framework for Health and Social Care Research, it is expected that valuable data arising from funded research should be made available to the scientific community. This must comply with participant consent and avoid inadvertent or deliberate identification of participants. De-identified data from this trial may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the lead author/Chief Investigator and Clinical Trials Unit.

19. DISSEMINATION POLICY

To communicate with academics and medical professionals the intention will be to publish a number of scientific papers in peer reviewed publications and also to present lectures and posters at national and international academic conferences.

The full trial dataset must be created and uploaded for publishing through the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database. This is in line with the European Commission's guidelines on posting and publication of result-related information within 12 months.

The final report to funder will be published in the NIHR Health Technology Assessment (HTA) journal.

Authorship will be based on the ICMJE recommendations and it is expected that members of the Trials Unit that managed the trial will be invited to be co-authors. Recruiting sites are not automatically granted authorship but will be acknowledged "on behalf of the ENHANCE-D investigators".

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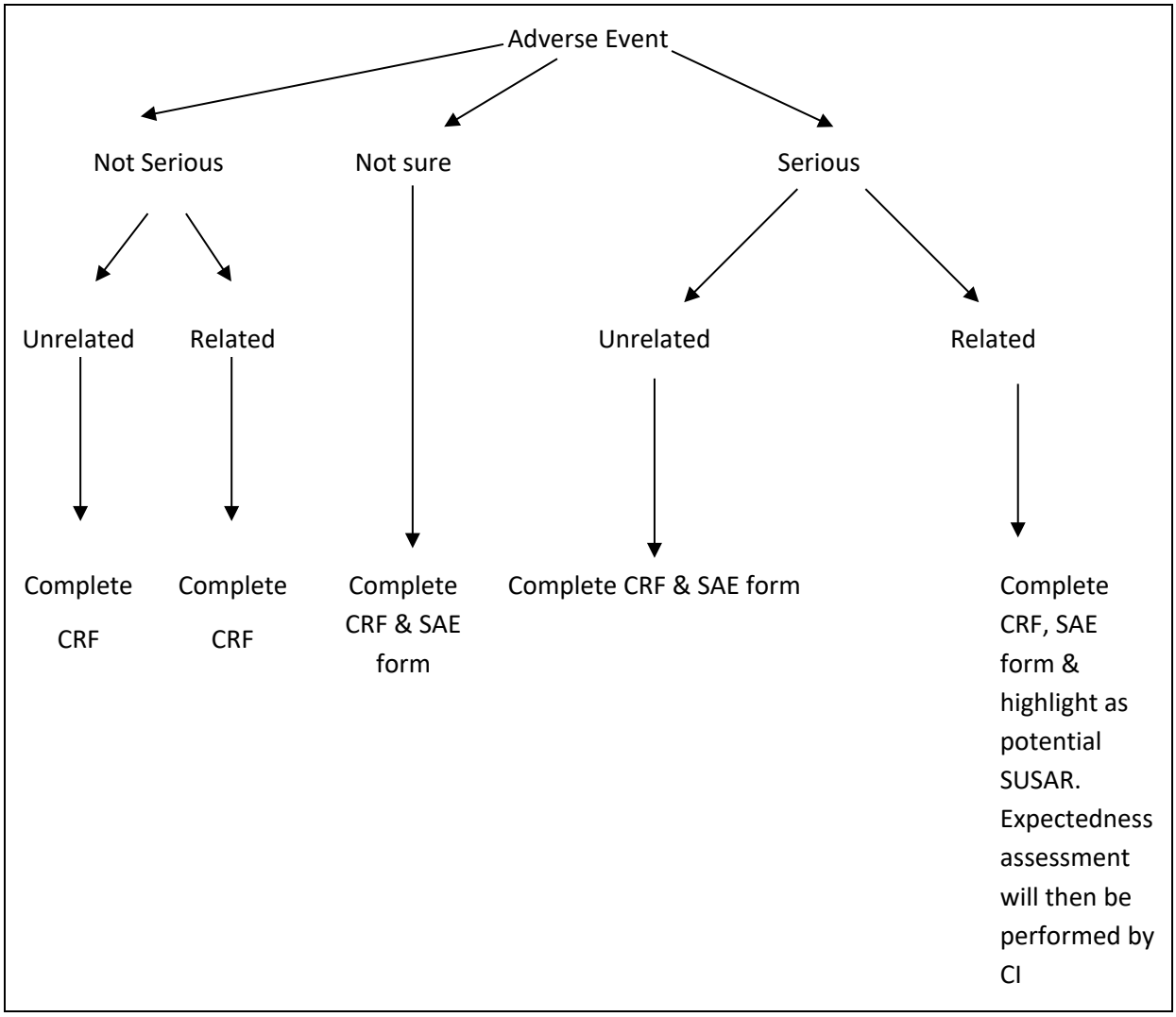
21. APPENDICES

21.1. Appendix 1 - Safety Reporting Diagram



{The diagram may require editing depending upon the requirements of the trial and the sponsor}

Contact details for reporting SAEs

Please send SAE forms to: **nctu.enhanced.sae@nhs.net**

21.2. Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made