A Randomised controlled trial to Evaluate the effectiveness and cost benefit of prescribing high dose FLuoride toothpaste in preventing and treating dEntal Caries in high-risk older adulTs (Reflect trial)

PROTOCOL

A UK Collaborative Trial funded by the Health Technology Assessment funding stream of the National Institute for Health Research

Sponsor

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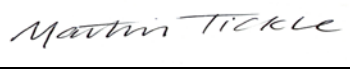
Signature

The CI confirms that the protocol will be conducted in compliance with the protocol, GCP, the Medicines for Human Use (Clinical Trial) Regulations 2004 (and subsequent amendments), the Data Protection Act 1998 and the Declaration of Helsinki.

Martin Tickle: 

Date: 15 September 2017

VERSION HISTORY:

Amendment no.	**Protocol version no.**	**Description of changes (*incl. author(s) of changes*)**	**Date Effective**
	Version 1	New Document	15/9/2017
	Version 1.1	Change of name of sponsor from Central Manchester University Hospitals NHS Foundation Trust to Manchester University NHS Foundation Trust, changed 3.3.1 identification of participants from Greater Manchester to England to allow recruitment from other geographical locations, amended appendix 2 to clarify qualitative interviews will be by telephone .	26/10/2017

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PROTOCOL SUMMARY

TRIAL TITLE	Randomised controlled trial to Evaluate the effectiveness and cost benefit of prescribing high dose FLuoride toothpaste in preventing and treating dEntal Caries in high-risk older adulTs (Reflect trial)
Clinical phase and Risk Adapted Category	Phase 4 This clinical trial has been assessed by the Sponsor as being Type A (the risk to participant safety in relation to the IMP is no higher than the risk posed by standard care)
Question addressed	What is the effectiveness and cost benefit of GDP prescribing of 5000ppm fluoride toothpaste compared to usual care in individuals 50 years and over with high-risk of caries
Eligibility criteria	Adults aged 50 years and over attending NHS dental practices who have a high risk of caries.
Interventions	1. Prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care. 2. Usual care only. (Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm)).
Outcome assessment	Primary outcome: Number and proportion of individuals requiring restoration or extraction or endodontic treatment due to caries. Secondary outcomes Clinical: Caries increment (mean DMFS), progression of early caries lesions using the International Caries Detection and Assessment System (ICDAS), Bleeding on Probing (BoP) measured by a dedicated team of calibrated and trained dental examiners, in a sub-group of the included participants. Patient: Oral health-related QoL (OHIP-14), health-related QoL (EQ5D), oral health behaviour, episodes of pain

	Economic: NHS and patient perspective costs, willingness to pay, net benefit (analyses over 3 year trial follow-up and modelled lifetime horizon).
Co-ordination	**Central**: by Trial Office in Aberdeen (Telephone 01224 438134) and Trial Coordinating Office Dundee (TCOD 01382 381213). **Overall**: by the Project Management Group, and overseen by the Trial Steering Committee and the Independent Data Monitoring Committee.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
AR	Adverse Reaction
AUC	Area under the curve
BID	Twice a day
BNF	British National Formulary
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTA	Clinical Trial Application
CTU	Clinical Trial Unit
DCE	Discrete Choice Experiment
DSUR	Development Safety Update Report
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
IB	Investigator Brochure
IDMC	Data Monitoring Committee
IMP	Investigational Medicinal Product
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NIHR	National Institute Health Research
NRES	National Research Ethics Service
OD	Once a day
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
PQ	Participant Questionnaire
QALY	Quality Adjusted Life Year
QID	Four times a day
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCOD	Trial Coordinating Office Dundee
TMF	Trial Master File

TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

TRIAL CO-APPLICANTS

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1 Professor Anne Marie Glenny
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9 Professor Iain Pretty
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11 Dr Tom Goodwin
12 Mr Paul McGarry

Project Management Group (PMG)

This group is comprised of the grant holders along with representatives from the Trial Office central trial team.

Trial Steering Committee (TSC) Members

The membership of this committee comprises independent members along with the Chief Investigator (CI) Professor Martin Tickle) or a nominated delegate. The other REFLECT grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Data Monitoring Committee (DMC) Members

This committee is comprised of independent members and the trial statistician contributes as appropriate. The CI and / or a delegate may contribute to the open session of the meetings as appropriate.

A Randomised controlled trial to Evaluate the effectiveness and cost benefit of prescribing high dose FLuoride toothpaste in preventing and treating dEntal Caries in high-risk older adulTs (Reflect trial)

1. INTRODUCTION

1.1 Background

The UK has an ageing population. The number of people of State Pension Age and over is projected to increase by 32.7 per cent from 12.4 million in mid-2014, to 16.5 million by mid-2039. Likewise the number of people aged 75 and over is projected to rise by 89.3 per cent, to 9.9 million, over the same period.(1) Whilst an increase in life expectancy should be celebrated, attention needs to be given to the complex health needs, including oral health needs, of the growing population of older people.

Dental caries is preventable, yet it is the most common disease worldwide. In high-risk older populations it is an important public health issue, as the number of older people who retain their natural teeth is growing rapidly. In England in 2009 6% of the adult population were edentulous, compared to 28% in 1978.(2) Dentate older adults tend to have extensively restored teeth,(2) mainly due to them having grown-up prior to the widespread use of fluoride toothpaste (introduced in the 1970's). For these older adults, the risk of developing dental caries increases due to the presence of restorations and prostheses (bridges or dentures) that increase plaque retention, dry mouth (often as a result of polypharmacy), exposed root surfaces and a cariogenic diet. The oral health of these individuals will decline as their physical and cognitive abilities deteriorate, resulting in a growing population health problem with significant financial repercussions for the NHS; so prevention of caries is important.(3)

Recent NICE guidance recognises the impact poor oral health can have on older individuals' ability to eat, speak and socialize.(4) This guidance focuses on those living in care homes (either nursing or residential) and highlights the lack of good quality evidence on the effectiveness of oral health interventions delivered to residents in care homes. Ongoing research aims to address this lack of evidence, with an NIHR funded feasibility study aiming to establish whether caries prevention through prescribed high-fluoride toothpaste is feasible, clinically effective and cost effective in a care home setting.(5) However, the majority of the 11 million adults, aged 65 years or over, live in their own homes, with less than 4% (approximately 414,000) living in some form of care home.(4) It is therefore important to establish a strong evidence base for the management of the oral health needs of older people across all residential settings.

1.2 Rationale for the trial

The current evidence to support prescription of high concentration fluoride toothpaste (specifically 5000 part per million (ppm) toothpaste) to prevent caries is weak.(6,7,8) The Cochrane review on different doses of fluoride toothpaste did not include any randomized controlled trials of 5,000ppm fluoride, however the review did find a dose-response relationship between the concentration of fluoride in toothpaste and caries prevention, with greater caries prevention for higher doses of fluoride.(8) This review is currently being updated to include adults: no trials on the prevention of coronal caries through the use of 5000ppm toothpaste have been identified. A more recent review of high fluoride concentration toothpastes included four studies (randomised and non-randomised) with 5,000ppm fluoride toothpaste.(9) None of these studies meet the inclusion criteria for the Cochrane review and all have significant design and methodological limitations. However, despite the weak evidence base, General Dental Practitioners (GDPs) are advised by national guidance to prescribe high concentration 2800/5000ppm fluoride toothpaste for older adults with active caries or at risk of developing

caries.(10) The use of this technology is expanding; in England in 2014 1.3 million items were prescribed at a cost of £17 million,(11) a 12.2% increase from the previous year; similar increases are evident in Scotland.(12)

We have little understanding of how this growing NHS investment benefits patients or can play a useful role in tackling an emerging public health problem. There is a need for clear, evidence-based guidance on the prescribing of high concentration fluoride toothpaste.

In preparation for this trial we have accessed routine data to better understand the current prescribing of high fluoride toothpaste (this helped inform our inclusion criteria with regard to the age of participants). We have also asked research active GDPs about what risk factors they consider when prescribing high fluoride toothpaste (these include caries rate, root caries, dry mouth, polypharmacy alongside social factors) and concerns they have over prescribing high fluoride toothpaste (duration of prescription was raised as an area of uncertainty). During these conversations, 21 GDPs expressed an interest in participating in research in this area. Based on our preparatory work, we propose a trial that will inform clinical guidance and policy on GDP prescribing of high concentration fluoride toothpaste for the purpose of caries prevention and treatment for a growing older population at increased risk of developing the disease.

2. TRIAL AIM and OBJECTIVES

Aim:

To evaluate the effectiveness and cost benefit of GDP prescribing of 5000ppm fluoride toothpaste compared to usual care in individuals 50 years and over with high-risk of caries

Primary objective:

- To compare the effect of prescribing 5000ppm fluoride toothpaste and usual care with usual care only on treatment for caries, including coronal/root restorations, endodontics or extractions
- To compare the costs and benefits, within a net benefit framework of prescribing 5000ppm fluoride toothpaste with usual care

Secondary objectives will evaluate the effect of prescribing 5000ppm fluoride toothpaste on caries (mean Decayed Missing Filled Surfaces [DMFS]) increment, progression of early caries lesions, bleeding on probing, quality of life (generic and condition specific), costs to the NHS and to individuals and society, oral health behaviour and episodes of pain. In addition, we will explore the attitudes of clinicians and patients to the prescribing and use of high fluoride toothpaste.

3. TRIAL DESIGN

A two arm, parallel group, pragmatic, open label Randomised Controlled Trial (RCT) with internal pilot comparing the clinical effectiveness and cost benefit of GDP prescribing of high concentration fluoride toothpaste compared to standard care in preventing and treating dental caries in older patients. The Medicines and Healthcare products Regulatory Agency (MHRA) has ruled that the trial should be categorised as a Clinical Trial of an Investigative Medicinal Product (CTIMP). In terms of the explanatory–pragmatic continuum, this trial design is more pragmatic than explanatory. We will therefore use an open-label, “real world” approach, in a natural setting, comparing prescription of high concentration fluoride toothpaste in accordance with National guideline recommendations (10) with usual standard of care. We consider the trial to be a Type A trial, as described in Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products.

A flow diagram is provided in Appendix 1. Follow up will last 3 years and will be conducted in multiple sites (up to 60 General Dental Practices) located in England, Scotland and Northern Ireland.

The design includes an internal pilot to assess recruitment of practices and participants, with pre-determined stop/go criteria to the main trial. In parallel with the pilot phase we will undertake a qualitative project to understand GDPs' practices and beliefs about prescribing 5000ppm fluoride toothpaste and patients' beliefs and experience of being prescribed 5000ppm fluoride toothpaste and perceived impacts on their oral health related behaviours. Furthermore, this element will also provide GDPs' and patients' feedback concerning recruitment to inform our recruitment strategy. The qualitative protocol is included as Appendix 2.

3.1 Intervention to be evaluated

5000ppm fluoride toothpaste prescription, used as prescribed by the participant's GDP informed by national guidance (10). The intervention is designed to reflect dental practice and therefore the frequency of prescription and the duration of the regimen will be determined by the patient's GDPs after assessing each patient's risk. We have restricted the intervention to 5000ppm fluoride toothpaste, as NHS prescribing data shows that 5000ppm is more commonly prescribed than the 2800ppm alternative. (13)

Current guidance recommends that for those adults with obvious active coronal or root caries dentists should prescribe high fluoride toothpaste.(10) Our inclusion criteria are less restrictive to allow for prescription based not just on caries activity but also based on other risk factors, as determined by the GDP. This approach is based on the hypothesis that 5000ppm fluoride toothpaste can prevent caries in those patients deemed to be high risk by their dentist, even though they don't present with 'obvious' caries. In our discussions with dentists this approach appears to reflect current practice.

The comparator will be usual care; advice given by the participant's GDP will be to buy 'standard', off-the-shelf 1350-1500ppm fluoride toothpaste and use as advised by their dentist informed by national guidance.(10)

Other recommendations in the national guidance (10) for self-administered (mouthwash) or professionally-applied (varnish) fluoride delivery methods could have an impact on the trial. We will take a pragmatic approach and leave the decision to use other fluoride delivery systems to the patients and their dentist, but the use of these interventions will be recorded.

3.2 Trial population

NHS dental patients, 50 years of age or older, attending a GDP who are considered by their dentist to be at high risk of developing caries.

Our decision to use the lower limit of 50 years of age is based on: high concentration fluoride toothpaste is currently being prescribed to individuals between 50 and 60 years;(13) individuals 50 years and over have grown up in the absence of widespread use of fluoride toothpaste and consequently many older adults have heavily restored dentitions increasing their caries risk;(2) the 2009 Adult Dental Health Survey suggests that those individuals with complex dental needs are most prevalent in late middle age.(3) Including a broad age range in the trial provides an opportunity to assess the impact of prescribing on different age groups in this older population.

High-risk individuals will be defined by: a diagnosis of active caries (into dentine) in the last 12 months which may/may not have been treated, or any root caries; and/or other risk factors as determined by their GDP. Participants can be living in any residential setting and receiving their dental care at a general dental practice.

3.2.1 Selection of participants

Participants will be assessed for inclusion by their GDP according to the trial inclusion and exclusion criteria.

3.2.2 Planned inclusion and exclusion criteria

Inclusion criteria: Inclusion criteria have been defined to ensure the participants in the trial are similar to those who would receive this intervention if it were part of usual care. We will focus on older patients with an increased risk of caries, more specifically people:

- aged 50 years or older
- with a diagnosis of active coronal caries (into dentine) in the last 12 months which may\may not have been treated, or any root caries; and\or other risk factors as determined by their GDP.
- receive their dental care in part or fully as an NHS patient
- living in any residential setting, and
- for whom their GDP decides prescription of high concentration fluoride toothpaste is appropriate for the patient

Exclusion criteria: People who:

- are currently prescribed (by GDP or GP) high concentration fluoride toothpaste (for GDPs prescription must have been issued at last examination visit)
- hypersensitivity for Sodium Fluoride and\or other ingredients used in 5000ppm toothpaste
- are living in the same household as someone already recruited to Reflect
- are unable to provide informed consent

3.3 Recruitment and Trial Procedures

3.3.1 Identifying participants

Recruitment will proceed in two phases, recruitment of practices and then recruitment of participants.

Recruitment of practices: An open invitation to practices within the three geographical areas will be distributed, requesting expressions of interest for participation in the trial. Following this expression of interest, and based on experience of recruitment to our previous HTA trials, we will conduct an appraisal of each practice's ability to recruit participants. This decision will also be informed by evidence of sufficient throughput of potentially eligible participants in the practices' electronic records. Practice principals will be local PIs and will be asked to identify a named designated trial coordinator and a deputy for the practice who will be responsible for administering the trial in the practice. All recruited practices will receive GCP and trial specific training and be reimbursed for their participation.

Recruitment of participants: Existing and new patients who fulfil the inclusion criteria will be invited to participate in the trial. Practices will use their patient records to pre-screen existing patients according to the eligibility criteria. Two different recruitment strategies may be used:

i) In Scotland, identified, potentially eligible participants will be sent a letter of invitation from their dentist along with a participant information sheet, starting with those patients who are closest to their next scheduled recall visit. Interested patients will be asked to phone their practice to make an appointment to discuss the purpose of the trial, what participation involves and check eligibility. The practice receptionists will block-book the potentially eligible patients into dedicated trial sessions. At this appointment, theGDP will take informed consent and perform baseline examination/data collection. Independent examiners will repeat the baseline clinical data collection and undertake a standardised caries assessment using ICDAS and BoP assessment.

ii) Alternatively, in England and Northern Ireland (where independent, standardised caries assessment will not be performed), practices may prefer to recruit on an ad hoc basis rather than block-booking. Potentially eligible participants will be

identified on a rolling basis, according to their scheduled visit. They will be sent a letter of invitation from their dentist along with a participant information sheet ahead of their appointment. Checking of eligibility, discussions regarding the purpose of the trial, taking of consent and baseline assessment/data collection will be as for i).

3.3.2 Informed consent

Potential participants will receive a letter of invitation and a trial information sheet detailing the process and procedures of the trial and the nature of the intervention to be tested. Dentists will take informed consent using a standardised consent form within the practices and will verbally reiterate the information contained in the information sheet and answer any questions that patients may have about the trial as part of the informed consent process.

3.3.3 Randomisation and allocation

Randomisation will be at patient level. Eligible and consenting participants will be randomised to one of the two intervention groups using the proven 24-hour telephone Interactive Voice Response randomisation application or via the web-based application, both hosted by CHaRT. The randomisation algorithm will use recruitment site, residential setting (own home/care home), exemption from dental treatment charges (yes/no) and age (50-65 years/over 65 years) as minimisation covariates to allocate treatment to intervention and control groups in a 1:1 ratio. A random element will be incorporated into the randomisation algorithm. The PI at site, or individual with delegated authority, will access the telephone or web-based system. Patient screening identification, initials and recruiting site (the stratifying variable) will be entered into the voice-activated or web-based system, which will return the allocation status. Participants will be informed of their allocated treatment group following randomisation.

The trial will be open label so neither the participant nor the participant's dentist will be blinded. The trial statistician and the study team will be blinded to the allocation during all analyses by use of a code to identify the two groups. The key to the code will be held by CHaRT.

Blinding of outcome assessment using the primary outcome will not be possible, as the participant's dentist will collect primary outcome data. A more detailed clinical examination undertaken by independent (external to the trial dental practices) dentists will be used to repeat primary outcome measures and collect secondary outcomes (caries increment and bleeding on probing). This more detailed clinical examination will take place in Scottish practices only and the independent examiners will be blind to the allocation. Source data verification will be undertaken according to the monitoring plan by:

1. Comparing the primary outcome measures with outcomes recorded in the clinical examination (Scotland only)
2. Comparing primary outcome measure in the Case Report Form (CRF) treatment provided for caries (coronal and root surfaces) including restoration, extraction endodontics) with centralised NHS treatment claims data for individual patients.
3. Source data verification audits in annual visits of each practice.

A clinical trials pharmacy will not be used to dispense the drug. The drug will be used as prescribed by the participant's GDP and as indicated by BNF. Participants will be expected to collect their prescriptions at a local community pharmacy. The intervention is designed to reflect contemporary dental practise and therefore the frequency of prescription and the duration of the regimen will be determined by the patient's GDPs after assessing each patient's risk. GDPs will provide instructions to each participant based on their assessment of risk and how they prescribe the drug.

3.3.4 Follow-up procedures

At baseline we will collect socio-demographic data on age, gender, eligibility for free prescriptions and free dental treatment and the participant's postcode. The GDPs will undertake a dental charting of the mouth to provide baseline oral health data.

Primary outcome:
The proportion of participants receiving any dental treatment due to caries; including restorations, endodontics or extraction. Any dental treatment provided and the reasons for providing treatment (caries or other e.g. trauma) will be recorded by the participant's GDP on the CRF at baseline and each subsequent visit. The primary outcome (restoration, endodontic treatment or extraction due to caries) will be extracted from the CRF.

Secondary outcomes (clinically assessed): The clinically assessed secondary outcomes will be measured in Scottish practices only; Appendix 3 provides a sub-protocol for this more intensive assessment of participants

- Coronal caries increment, including dentist replacement restorations for caries, at tooth surface (DMFS) level by independent, trained and calibrated, clinical examiners at baseline and 3 year (+/- 3 months) follow-up. We will use the ICDAS method (14) to assess caries as it provides flexibility to analyse and present caries data at different diagnostic thresholds.
- Root caries increment, including dentist replacement restorations for caries, at tooth surface (DMFRS) level by independent, trained and calibrated, clinical examiners at baseline and 3 year (+/- 3 months) follow-up.
- Early caries lesion progression data, using ICDAS.
- Bleeding on probing (BoP) will also be recorded by the independent clinical examiners. BoP provides evidence of long term optimal brushing rather than transitory measures such as visible plaque scores.(15)

Secondary outcomes (patient reported):

- Oral health status using OHIP14, a measure of oral health-related Quality of Life (QoL), collected at baseline and annual follow up through patient administered questionnaires. The OHIP-14 is the most common, validated dental quality of life instrument and has been successfully used in previous HTA trials. It has been found to be sensitive to differences in oral health and is closely correlated with self-reported oral health outcomes (16)

- The EQ-5D-5L profile measure of generic health status,(17,18) will be collected at baseline and annual follow up through patient questionnaires.

- Any episode of dental pain (and total number per participant) during the 3 year follow up period severe enough to trigger seeking advice from a healthcare profession (dentist, GP, community pharmacist). This will be recorded at scheduled and unscheduled dental visits by patient questionnaire included in the CRF.

- Oral health behaviour, including self-reported brushing/other sources of fluoride. Evaluated at baseline and through annual questionnaires sent by mail to the home address of participants.

Routine data:

- Fulfilment of prescriptions will be measured via Business Services Authority (BSA), Business Services Organisation (BSO) and Information Services Division (ISD) datasets. Adherence to the allocated intervention (prescription of 5000ppm) will also be explored in the qualitative element of the study.

Economic outcomes:

- Provision of NHS and private dental treatments will be collected from the CRF. In addition we will also collect information on NHS treatment completed using routinely collected data held by the Information Services Division (ISD) of NHS National Services Scotland, Business Services Authority (BSA, England) and Business Services Organisation (BSO, Northern Ireland). These datasets detail all NHS treatments provided to patients in Scotland / Northern Ireland and all tariffs paid to dentists for

bands of treatment in England. Treatment cost data will be collected for participants from one year prior to randomisation until the end of the trial.

- All remaining resource use data will be collected using questionnaires provided to participants on attendance for dental care or mailed to participants who fail to attend. These will include the use of other NHS healthcare services (e.g. GP visits, dental hospital attendances and other healthcare resource use) directly related to dental problems as well as data on non-NHS costs (e.g. time and travel costs, time off work, privately purchased care, self-purchased dental care products).
- We will collect OHIP14 and the EQ-5D-5L health profile measure at baseline and each follow up time point in the trial via postal questionnaire. Collection of EQ-5D-5L will enable the calculation of the mean cost per additional QALY as a secondary health economic outcome.
- A discrete choice experiment (DCE) with an online representative sample of the UK general population (aged 50 and over) will be undertaken to elicit willingness to pay (WTP) for high fluoride toothpaste and associated patient relevant outcomes. A further sub-protocol, including questionnaires for the general population DCE will be submitted to a university ethics review board in due course.
- Long term economic evaluation with trial results extrapolated over a life-time horizon using Markov modelling methods.

3.3.5 Change of Status/Withdrawal procedures

Participants will remain in the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status with the exception of complete withdrawal of consent will mean the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal will be retained and used in the analysis. Participants randomised to 5000 ppm fluoride toothpaste who stop trial medication or participants randomised to routine care but who purchase or otherwise receive high fluoride toothpaste are not considered as having withdrawn from the trial. When a participant completely withdraws from the trial this will be documented in a participant withdrawal form signed by the relevant PI (the participant's GDP) with a copy stored in the participant's CRF locally and a copy sent to the trial manager to be stored in the TMF.

4. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

This will be an open label trial and GDPs and participants will not be blind to the allocation. This is a pragmatic trial; the intervention will be prescription of 5000 ppm fluoride toothpaste by the participant's GDP.

4.1 Trial drug

The Investigational Medicinal Product (5000 ppm fluoride toothpaste) will not be specified by manufacturer or individual product. A pharmacy will not be involved in the trial. The frequency and duration of prescription of the toothpaste will be at the discretion of the participant's GDP depending on their assessment of their patient's risk. Compliance in terms of a) redeeming prescriptions and b) use of the toothpaste as advised by the GDP will be at the discretion of the participant. The comparator will be usual care; advice given by the participant's GDP will be to buy 'standard', off-the-shelf 1350-1500ppm fluoride toothpaste and use as advised by their dentist informed by national guidance.(10)

4.1.1 Participants' Compliance

Compliance will depend on the GDPs' and participants' behaviour, the trial team will not seek to ensure a minimal level of compliance. Compliance will be assessed to determine its impact on trial outcomes. This will be done by:

1. GDP's issuing of prescriptions, number of tubes prescribed and date of each prescription recorded in the trial CRF
2. Participants' re-deeming prescriptions via national dental prescribing datasets held by BSA, BSO and ISD

3. Participants (both test and control groups) reported use of toothpaste through mailed self-report questionnaire
4. Toothbrushing (not necessarily using 5000 ppm fluoride toothpaste and 'standard' toothpaste) through BOP clinical assessment (Scotland only).

4.1.2 Concomitant Medications

Other drug(s) that may be taken during the trial will be recorded in the CRF. Prescription of any other high fluoride toothpaste product is prohibited during participation.

4.1.3 Summary of Product Characteristics and Reference Safety Information

A particular product will not be specified for prescription in the trial; the product, the amount and frequency of prescription will all be determined by the dentist on an individual basis according to an assessment of each patient's caries risk. The 5000ppm fluoride toothpaste will be used as per its licensed indications. Contraindications include hypersensitivity for Sodium Fluoride and\or other ingredients used in 5000ppm toothpaste (liquid sorbitol (non-crystallising), dental type silica, dental type silica (precipitated), macrogol 600, tetrapotassium pyrophosphate, xanthan gum, sodium benzoate (E211), sodium laurilsulfate, spearmint flavouring (containing peppermint oil, carvone, spearmint oil, menthol, anethol, and lemon oil), saccharin sodium, brilliant blue FCF (E133) and purified water). Expected side effects include in some rare cases (i.e. less than 1 in 1000 people treated) hypersensitivity reactions e.g. rash, itching swelling and redness. Burning oral sensation has also been reported.

The Reference Safety Information for this trial, for the purposes of assessing the expectedness of events considered to be related to the IMP will be section 4.8 'undesirable effects' of the SPC for Morningside Healthcare Ltd. Fluoride 5000 ppm Toothpaste dated 22nd July 2015.

5. SAFETY

The Sponsor and CI have undertaken an initial risk assessment which will be periodically reviewed and if necessary updated as the trial progresses. The Sponsor has concluded that this is a low risk trial, as the drug is being prescribed by GDPs as per its licensed indications and dispensed by community pharmacists. It is topically administered and the known side effects are rare and minor in nature.

5.1 Definitions.

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each AE will be considered for severity, causality and expectedness and may be reclassified as a serious adverse event or reaction based on prevailing circumstances.

Adverse events are not:

- continuous and persistent disease or symptom, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied; or
- treatment failure (caries development)

An **adverse reaction** (AR) is any untoward and unintended response in a participant to an investigational medicinal product which is considered to be related to that product at any dose.

An **unexpected adverse reaction** (UAR) is an adverse reaction that is not consistent with the product information in the summary of produce characteristics (SPC).

A **serious adverse event** (SAE), **serious adverse reaction** (SAR) or **suspected unexpected serious adverse reaction** (SUSAR) is any AE, AR or UAR respectively that at any dose:

- results in death;
- is life threatening (i.e. the subject was at 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);

- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect,
- Is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

REFLECT Trial specific expected adverse reactions:

In this trial the following events are potentially expected and will be recorded and reported:

MHRA guidance on 5000 ppm states that '*In some rare cases (i.e. less than 1 in 1000 people treated) allergic (hypersensitivity) reactions can occur e.g. rash, itching swelling and redness. Burning oral sensation has also been reported*'.

5.2 Procedures for detecting, recording, evaluating and reporting ARs, SARs

5.2.1 Detecting ARs and SARs

SARs will be recorded from the time a participant consents to join the study until the end of their follow up. The local investigator (GDP) will record in the CRF all directly observed ARs and all ARs spontaneously reported by participants which have a possible causal link to the IMP. In addition, each trial participant will complete a questionnaire at each attendance and one sent annually to their home, which collects information of ARs and SARs. In addition, as part of the informed consent process, participants will be asked to report any ARs and SARs to their dentist that they feel could be related to the IMP on an ad hoc basis.

5.2.2 Recording ARs and SARs

Information on ARs must be evaluated by each participant's dentist (Principal Investigator) and recorded on Case Report forms. Once causality has been evaluated, SARs and SUSARs will be captured on an SAR form. In addition death for any cause (related or otherwise) is recorded on the SAR form.

In this trial, a pre-existing condition (i.e., a disorder present before the AR reporting period started and noted on the pre-treatment medical history form) should not be reported as an AR unless the condition worsens or episodes increase in frequency during the AR reporting period.

5.2.3 Evaluating ARs and SARs

Seriousness, causality, severity and expectedness should be evaluated.

Assessment of Seriousness

The local investigator should make an assessment of seriousness as defined in Section 5.1.

Assessment of Causality

Each AR/SAR should be clinically assessed for causality based on information available and reviewed as new information becomes available. i.e. relationship of AR to the trial medicament. For the purpose of this trial the relationships will be defined as follows: Definitely, Probably, Possibly, Unlikely, Not Related. All ARs/SARs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the trial drug will be considered as ARs/SARs.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Severity

The PI should make an assessment of severity for each AR/SAR and record this on the SAR form according to one of the following categories:

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 5.1). If an event is judged to be an AR/SAR/SUSAR, the evaluation of expectedness will be based on the relevant product information documented in the trial's Reference Safety Information (Section 4.1.3).

Follow up of Adverse Reactions

All recorded ARs that meet the criteria for recording and reporting will be followed until they are resolved or the investigator assesses them as chronic or stable or the participant's participation in the trial ends (i.e., until a final report is completed for that participant). In addition, all SARs and those non-serious events assessed by the investigator as possibly related to the drug should continue to be followed even after the participant's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as chronic or stable. Resolution of such events is to be documented on the case report form.

5.2.4 Reporting ARs and SARs

Reporting responsibilities of the PI

Once the Investigator becomes aware that an SAR has occurred in a study participant, they must report the information to the Trial Office within 24 hours of becoming aware of the event, the Trial Office will report to the Sponsor within 24 hours of becoming aware of the event. The SAR form must be completed as thoroughly as possible with all available details of the event, and signed by the Investigator or designee. If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

Reporting responsibilities of the CI

To report an SAR to the Trial Office, the Investigator can either complete a hard copy of the SAR form and email or fax it to the Trial Office, or complete the SAR form on the study website. If the SAR form is completed on the study website the trial manager will be automatically notified. If, in the opinion of the PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the Sponsor within 24 hours of receiving the signed SAR notification. The Sponsor will delegate assessment of SARs to the CI. If the CI judges an event to be a SUSAR then he will report it accordingly. The Sponsor cannot downgrade an assessment from the PI or CI. If the CI wishes to downgrade an assessment from the PI, the PI's agreement to the revised assessment must be obtained and the discussion documented. Any disparity will be resolved by further discussion between these parties – the discussion will be documented.

If all the required information is not available at the time of reporting, the CI must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

5.2.5 Regulatory reporting requirements

An annual Development Safety Update Report (DSUR) will be submitted to the MHRA and the main REC listing all SARs and SUSARs. The DSUR must be prepared as a collaborative process between CI and the sponsor. It is expected that the CI will demonstrate substantial input into the

preparation of the DSUR. The DSUR must be reviewed and authorised for submission by both the sponsor and the CI prior to sending to the MHRA and REC

The Sponsor is responsible for informing the MHRA and the main REC of safety events requiring expedited reporting. Fatal or life threatening SUSARs will be reported to MHRA no later than **7 calendar days** and all other SUSARs will be reported no later than **15 calendar days** after they are first aware of the reaction.

6. OUTCOME MEASURES

6.1 Primary outcome measure

Number and proportion of participants requiring restoration or endodontics or extraction of one or more teeth due to caries

6.2 Secondary outcome measures

Clinical: Coronal caries increment (DMFS), Root caries increment (DMFRS), progression of early caries lesions, bleeding on probing (BoP). DMFS, progression of early lesions (measured using ICDAS) and BoP will be measured by a dedicated team of calibrated and trained dental examiners, in a sub-group of the included participants. (Measured in Scotland only)

Patient: Oral health-related QoL (OHIP-14), health-related QoL (EQ5D), oral health behaviour, any and number of episodes of pain severe enough to trigger an unscheduled visit to a healthcare profession (dentist, GP, community pharmacist)

Economic: NHS and patient perspective costs, willingness to pay, net benefit, long-term cost-effectiveness

7. DATA COLLECTION AND PROCESSING

7.1 Measuring outcomes

Outcomes will be measures using a variety of methods including; baseline information form to be completed by the dentist and baseline questionnaire by the participant, dentist completed CRF at each attendance of the participant, a patient reported questionnaire administered when participants attend the Practice an annual postal questionnaire sent to all participants, access to national NHS dental activity data sets, and clinical examinations by independent and blinded examiners (Scotland only).
For any participant that fails to attend elective or non-elective visits to the dentist over the 3 year follow up, all efforts will be made to collect clinical outcome data and questionnaires will be posted.

7.2 Schedule of data collection

	Baseline	**Elective and non-elective visits to the dentist over 3 year follow up[1]**	**Annual Questionnaire**	**National Database**	**36 months**
Clinical Status (full dental chart)	○				
Treatment details **Check ups, restorations,**	○	○			X

	Baseline	Elective and non-elective visits to the dentist over 3 year follow up[1]	Annual Questionnaire	National Database	36 months
endodontics, extractions (reason for treatment in CRF and all NHS treatments in national datasets) **Prescription of toothpaste (date and amount prescribed)** **Relevant medical history and medication**					
Healthcare costs **GDP completed CRF: payment mechanism (NHS/private) and charges levied** **Dental treatment received in other settings (patient element of CRF)** **NHS costs from national data sets** **Non NHS treatment costs in patient element of CRF)**	○	○			○X
Detailed independent clinical assessment ICDAS, BoP (Scotland only)	○				○
EQ-5D-5L	○		●		
OHIP-14	○		●		
Pain - seeking professional care because of pain	○	○			
Oral health behaviour	○		●		
Redemption of toothpaste prescriptions					X

	Baseline	Elective and non-elective visits to the dentist over 3 year follow up[1]	Annual Questionnaire	National Database	36 months
Adverse reactions		○			

[1] **dentists should invite participants to attend practice at least once a year**

○ Dental Practice – CRF (includes both GDP and participant completed elements)

● Postal Questionnaire

X NHS centralised dental databases;

7.3 Data processing

Data collected in the practices will use paper CRFs – which will be photocopied and copies mailed to the CTU by signed for delivery. CRF data will be entered onto the trial database in the CTU. Staff in the Trial office will work closely with PI and designated trial coordinators in each practice to ensure the data are as complete and accurate as possible. Postal questionnaires will be sent out by the CTU. Responses will be sent to the CTU for data entry. A single reminder letter and follow-up questionnaire will be sent out to non-responders. Extensive range and consistency checks will further enhance the quality of the data.

8. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

Sampling methods and rationale:

Based on data on current prescribing patterns in Scotland, we know that only 40% of GDP practices are prescribing high fluoride toothpastes and that 80% of the prescribed high fluoride toothpaste (2800ppm and 5000 ppm) is prescribed by only 20% of dentists.(13) However, the proposed trial will be open to all GDP practices with NHS patients, irrespective of current prescribing behaviour. We will endeavour to include a mix of independent and corporate practices, acknowledging the increasing trend towards high street practices owned by corporate bodies.

High-risk potential participants will be initially identified through examination of the clinical database within each practice. The majority of adults, aged 65 years or over, live in their own homes, with less than 4% living in some form of care home. However, participants will be eligible for inclusion irrespective of their residential setting.

8.1 Sample size

The sample size calculation is based on a meaningful absolute target difference of 10% (75% vs 65%) in the primary outcome measure. This difference is considered to be both a realistic and important difference from discussion with dentists, PPI groups and from published estimates.(6,7) The value for the comparator group (75% of individuals allocated to standard care who have restoration(s) or extraction(s) due to caries during the 36 months of follow up) is based on published data and Scottish treatment data.(19) For the proposed target difference, a two-sided 5% significance level, and 90% power, 440 participants (880 in total) will be required to provide data for the primary outcome at 36 months. Based on our previous and current HTA trials, we are assuming 25% attrition, and so 587 participants per group are required (1174 in total) in 60 practices (each practice recruiting an average of 20 participants). Based on an estimated consent rate of 50% (data from IQuad,20), 2348 eligible patients will be invited to participate.

An important secondary outcome within our proposed trial is caries increment, measured using the number of Decayed Missing and Filled tooth Surfaces (DMFS). Using the mean number of Decayed Missing and Filled tooth Surfaces (DMFS), the caries increments for an older population in the published literature vary, but there seems to be consensus around one surface per year.(21) Given the fact that the standard deviations approximate the means in

terms of caries increment, a reduction in caries increment from 3 to 2 surfaces with the intervention would produce a ~30% reduction in caries increment with the intervention over three years. The numbers needed to adequately power this secondary outcome are relatively small compared with the primary outcome measure:
For secondary caries outcomes, group sample sizes of 200 and 200 achieve 97.5% power to reject the null hypothesis of equal means when the population mean difference DMFS increment is μ1 - μ2 = 2 - 3 = -1.0 with standard deviations of 2 for group 1 (intervention) and 3 for group 2 (control), and with a significance level (alpha) of 0.05 using a two-sided two-sample t-test allowing for unequal variances. Assuming 25% attrition, 267 participants per group are required (534) in total in 28 practices. Based on an estimated consent rate of 50% 1068 eligible patients will be invited to participate. Further details of the evaluation of the secondary caries outcome measures is presented in a sub-protocol for Scottish practices (Appendix 6)

8.2 Recruitment rates and Milestones

Our recruitment projection is based on recruiting up to 60 active centres in the 3 localities (28 in Scotland; 16 in Manchester and 16 in Northern Ireland) participating across a 13 months recruitment period with the expectation that they will contribute a maximum of 20 participants per practice/month in Scotland and 6 participants per practice/month in Manchester and Northern Ireland, this is reflected in the different recruitment processes set out above.

We will undertake a 9 month internal pilot, which will start at day 1 of the programme (this includes the first 3 months set up of the trial). We intend to start recruitment of practices in month 4 and recruitment of participants will begin in month 5 of the project. The internal pilot is primarily designed to demonstrate that recruitment is possible and at a rate inline with our estimated milestones and costs. The specific objectives of the internal pilot are to assess recruitment of practices and participants and monitor the representativeness of participants. At the end of the internal pilot we will consider whether an adjustment to the number of practices is required, as larger practices may be able to recruit more efficiently.

During the internal pilot phase we anticipate a single decision point at the end of the first 5 months of participant recruitment. By the end of month 9, 24 practices should have been recruited, 51 practice months of recruitment should have occurred and 322 participants should have been randomised.

A green/amber/red approach to progression at month 9 has been included in the trial. The criteria are based on targets of 24 recruited practices at month 9, recruiting an average of at least 6 participants per month:
- Green: 100% of target recruitment achieved and average at least 6 participants per month - automatic progression.
- Amber: 50-100% recruitment achieved - identify remediable factors and submit recovery plan to the funder with new targets for the following 6 months.
- Red: less than 50% recruitment achieved - stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed.

9. STATISTICAL ANALYSIS

A Detailed Statistical Analyses Plan (SAP) will be produced which will include, but not be limited to the investigational plan and study design, listing of outcomes, timing and objectives of internal pilot and final analysis including effectiveness evaluations. The SAP will set out the summary measures to be reported; methods of analysis, plans for handling missing data, non-compliance and withdrawals, the timing and frequency of analyses, and use of intention to treat analysis.

Demographic and other characteristics of participants

Demographic (age, sex, ethnicity) and baseline characteristics (DMFT, DMFS, concomitant illness / treatment, exempt\not exempt from NHS dental charges) will be summarised and

displayed in tables for all randomised patients. In addition, mean NHS treatment costs in the 12 months prior to recruitment will be included in the baseline characteristics tables. Frequency counts and percentages will be used to present categorical data. Number of patients, mean, mode, median, SD, minimum, maximum and IQR will be used to present continuous data.

The primary outcome measure will be analysed using a generalised linear model with adjustment for the minimisation variables (recruitment site, residential setting, exemption (including partial exemption) from dental treatment charges and age band). Secondary outcomes will be analysed using generalised linear models with adjustment for minimisation and baseline variables when available. Statistical significance will be at the 2-sided 5% level with corresponding confidence intervals derived. Subgroup analyses on the primary outcome will explore the possible modification of treatment effect by clinically important factors; gender, age and NHS dental charges exemption status. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses. All analyses will initially be performed on an intention to treat basis, although we will consider additional analysis groups such as per-protocol for investigation of adverse events. The main statistical analyses will be based on all participants as randomised, irrespective of subsequent compliance with the treatment allocation; this will be detailed in the SAP.

From the internal pilot phase we will report estimates of recruitment rates and potential participant availability, together with appropriate confidence intervals. Outcome data will not be imputed for the primary analysis, but score data for participants who have missed a scheduled questionnaire will be estimated using a multiple imputation approach to make use of partial outcome data. Sensitivity analyses will be conducted to assess the robustness of the treatment effect estimate to these approaches. Missing items on the health-related outcome measures will be treated as per the instructions for that particular measure. There are no planned interim outcome analyses; all analyses will occur following completion of trial follow up. Interim analyses will be performed only if requested by the Independent Data Monitoring Committee

Safety evaluation
Analysis of adverse reactions or serious adverse events will be undertaken on a per protocol basis. The nature and frequency will be described and tabulated.

10. ECONOMIC EVALUATION

A full economic evaluation will be conducted as part of this study:

1. At three years of follow up, alongside the primary RCT outcome measure, and
2. Based on an extrapolation of trial outcomes over a patient's life-time, using an appropriate Markov decision analysis model to explore longer term cost-effectiveness.

The primary economic evaluation will be in the form of a cost-benefit analysis, reporting net benefit (Willingness To Pay (WTP) - cost), with WTP elicited using a Discrete Choice Experiment (DCE). We have chosen a cost-benefit analysis (CBA), as opposed to a traditional analysis of cost per generic EQ-5D QALY as the primary economic outcome measure because of concerns that generic QALYs are not sufficiently sensitive to capture the processes and outcomes of dental treatments. The CBA is therefore the outcome of most interest in terms of investigating value for money (efficiency) of prescription of high concentration fluoride toothpaste. In addition to the primary health economic analysis, two further analyses will be undertaken as secondary economic outcomes to inform various stakeholders:

- NHS decision makers, such as NICE may be interested in the cost of achieving gains in quality adjusted life years (QALYs) and therefore recommend the conduct of a cost per QALY analysis for technology appraisal. In order to comply with these recommendations, we will include the generic EQ-5D-5L health profile measure at baseline and each follow up time point in the trial. This will enable the calculation and presentation of the mean cost per additional QALY as a secondary health economic outcome.

- Dental practitioners may be interested in the cost of achieving various specific clinical outcomes. We will therefore complete a cost-effectiveness analysis, based on the primary clinical outcome measure for the trial, reporting cost per episode of dental treatment avoided (i.e. the cost per filling or extraction avoided). A further secondary analysis will present cost per DMFS avoided.

Estimation of costs:
Costs will be estimated from both an NHS and patient perspective. NHS costs of providing the high fluoride toothpaste intervention will be based on the costs of dispensed prescriptions verified by BSA, BSO & ISD in England, Northern Ireland and Scotland respectively. Methods for the collection of resource use data for cost estimation over the trial follow up are outlined in Section 7. All resource use data will be costed at the patient level, using region specific tariffs, and aggregate costs applied across these three settings, with sensitivity analyses presenting data for each setting separately.

Data on costs for each area of service use will be summed to provide a mean cost per patient participant (from both an NHS and patient perspective). Incremental costs per patient for high dose fluoride toothpaste vs usual care will be estimated using generalised linear models with appropriate distributions for cost data and adjustment for baseline covariates, such as gender and age. The costing analysis will include a statement on budget impact of alternative policy approaches.

Cost-Benefit Analysis – willingness to pay (WTP):
Whilst health based outcomes are of importance for funders of dental care, there is a growing interest in wider measures of value, which go beyond traditional QALY approaches and offer a more holistic and sensitive measure of value. It is crucially important for adherence, and hence real-world cost-effectiveness, that any public health intervention is not only valued in terms of health outcomes within a clinical trial, but also has wider generalisability to the consumers of the intervention. We will therefore conduct a cost-benefit analysis (CBA) reporting benefits in terms of WTP to obtain a more holistic measure of value. WTP will be obtained from a discrete choice experiment (DCE),(22) conducted with a nationally representative sample of the general population (aged 50 and over), to explicitly value the provision of high fluoride toothpaste, together with a range of plausible outcomes from the trial (e.g. avoidance of caries progression). The DCE will explicitly value the high fluoride toothpaste intervention, together with associated health outcomes and other important attributes.

The DCE will include a cost attribute. By including this attribute, the willingness to pay (WTP) for a change in the level of any other attribute will be estimated. A detailed sub-protocol for the general population DCE, including all relevant paperwork and questionnaires will be submitted to a University ethics committee. Estimates of WTP derived from the DCE will be combined with the intervention (provided or not) and clinical outcome data from the trial to report net benefit (mean WTP – mean cost 23) for high fluoride toothpaste compared to standard care. If benefits are greater than the costs, then high fluoride toothpaste would be deemed an efficient use of resources.

Results will be presented on a cost-benefit plane, illustrating the probability that the intervention is associated with positive or negative net benefit. A comprehensive set of sensitivity analyses will be undertaken to explore uncertainty in our conclusions. These will include assumptions surrounding missing data, the estimation of costs and the effect of different payment / co-payment structures on the cost-benefit results.

Decision Modelling:
The “within trial” economic analyses will assess and report on the costs and outcomes of high fluoride vs. standard treatment up to 3 years post-randomisation. However, the true economic value of an intervention depends on the long-term implications of that intervention. We will develop a *de novo* Markov decision analysis model, to extrapolate the trial outcomes over a longer, life-time horizon.(24) Results will be reported using a cost-effectiveness framework and

estimates of WTP from the DCE will be used to explore results using a similar cost-benefit framework to that used for the primary trial based economic analysis. The final model structure and health state definition (e.g. caries progression, new caries, and tooth loss) will be developed in conjunction with dental experts. National cohort datasets, such as the adult dental health survey, and other longitudinal studies will be used as a source of baseline transition probabilities. Sensitivity analysis will use the data from the control (standard care) arm of the trial. Where possible, survival analysis methods will be used to assess the time to transition between health states in each of the study arms, with survival curves fitted over an extended time frame (patient's life time). Data from cohort studies and literature reviews will be used where necessary to supplement extrapolation models to determine long run caries progression.

Cost data for health states beyond trial follow up will be sourced from the trial data and routine data sources (ISD/BSA/BSO) for appropriate treatment in the respective model health states. To inform a life-time cost-benefit analysis, estimates of WTP will be sourced directly from the DCE conducted alongside the trial for specific health states (e.g. WTP to avoid caries progression, new caries or tooth loss). The model will be developed at an early stage in the study to ensure all relevant data to populate the model are collected within the trial. All modelling assumptions will be extensively tested using sensitivity analyses and the model will be fully probabilistic. Key gaps in the evidence base will be identified and their potential impact on cost-effectiveness explored. Results will be presented using standard economic evaluation approaches to illustrate uncertainty. Threshold analyses will be conducted to indicate the values required for key model parameters to change economic evaluation results. Patients will be consented to obtain longer term data linkage to routine records, which can then be used for future validation of the extrapolation assumptions.

11. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 Arrangements for day-to-day management of the trial

The trial will be co-ordinated from the Trial Co-ordinating Office (TCOD) based in the Dundee Dental School and Hospital, University of Dundee and the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen. TCOD will provide day to day support to the GDPs and outcome assessors/research nurses. CHaRT, Health Services Research Unit, Aberdeen University will provide the database applications and IT programming host the randomisation system, co-ordinate the patient follow-up questionnaires, provide experienced trial management guidance, and take responsibility for all statistical aspects of the trial (including interim reports to the TSC and DMC.

The Trial Office Teams at TCOD and CHaRT will meet formally approximately monthly during the course of the trial to ensure smooth running and trouble-shooting. We intend to produce a yearly Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

11.2 Local organisation in sites

PIs will be practice principals (practice owners – or lead dentists in the case of corporate practices). Practices will appoint a named trial coordinator plus a deputy (to cover for periods of absence) as the designated link person for all communication with the research team. The practices will:

1. Undertake GCP and trial specific training as appropriate
2. provide access to practice databases for initial screening of patients for eligibility
3. send out letters of invitation and trial information sheets to potentially eligible patients
4. check eligibility, including caries risk and take informed consent
5. contact CTU for randomisation and complete web-based randomisation procedure
6. prescribe 5000ppm for test group patients
7. collect data as required in the CRF

8. assess and report SARs
9. provide access to practice for trial monitoring purpose

11.3 Project Management Group (PMG)

Oversight of the operational management of the trial will be supervised by the Project Management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. The research team has the expertise to cover the clinical aspects of the research.

11.4 Trial Steering Committee (TSC)

The trial is overseen by a Trial Steering Committee (TSC) appointed by the funder. The membership of this Committee is comprised of independent members along with the Chief Investigator. The trial Sponsor, other grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. Details of the membership of the TSC can be found at the start of this protocol. The TSC will meet approximately yearly.

11.5 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be convened and appointed by the funder, one of whom is an experienced statistician. After the trial has been initiated the IDMC will initially meet to agree its terms of reference and other procedures.

The committee will meet regularly as required to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

12. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

12.1 Research Governance

The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This will aid compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The Sponsor and CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the trial (compliance with appropriate governance) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial.

12.2 Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participants' details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The CTU senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

12.3 Sponsorship

Manchester University NHS Foundation Trust is the sponsor for the trial.

13. ETHICS AND REGULATORY APPROVALS

The (to be completed after favourable opinion has been received) Research Ethics Committee has reviewed this trial. The trial will be submitted to the MHRA under the notification scheme for risk-adapted clinical trials of Investigational Medicinal Products. The trial will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Annual progress reports, notification of End of Trial, and a final report at the conclusion of the trial will be submitted to REC and to the MHRA within the timelines defined in the regulations.

14. QUALITY ASSURANCE

The trial will be monitored to ensure that the trial is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan determined by the risk assessment. Audit: A Quality Assurance (QA) activity to ensure that systems are achieving the standards set, including highlighting any failures that have not been identified through quality control (QC). Monitoring is a Quality Control procedure.

14.1 Direct Access to Data

The agreement with each PI will include permission for trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. Consent from participants for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.2 Monitoring arrangements

The purpose of trial monitoring as defined in ICH GCP is to ensure that:
1) the rights and well-being of trial participants are protected;
2) the reported trial data are accurate, complete, and verifiable from source documents;
3) the conduct of the trial is in compliance with the currently approved protocol/amendments, with GCP, and with the applicable regulatory requirements.

This trial will take a risk-based approach to monitoring focusing on the most critical safety and data elements. The Sponsor will complete, periodically review and if necessary update a trial risk assessment outlining any potential hazards of the trial and proposal on how to minimise them. The extent of monitoring for the trial is based on the Sponsor's risk assessment. Monitoring will be an ongoing activity from the time of initiation until closeout and will comply with the EU directive 2001/20/EC and ICH and GCP regulations. All monitoring activities will be documented. Site monitoring visits will be carried out according to an agreed monitoring plan and available SOPs held in the Trial Master File.

14.3 Risk assessment

An independent risk assessment has been carried out by the Sponsor prior to commencement of the trial and reviewed and, if necessary, updated annually for the duration of follow up. The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations. The approach to, and extent of, monitoring will be specified in a trial monitoring plan which will be determined by the risk assessment of the study and updated if necessary following the outcomes of the annual risk assessment review.

15. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme. The Sponsor will provide indemnity for non-negligent harm. All dentists and dental care professionals working on the trial must be registered with the General Dental Council and have appropriate indemnity arrangements in place.

Research costs will be met by a grant from the Health Technology Assessment funding stream of the National Institute of Health Research. The contract holder for the grant will be l Manchester University NHS Foundation Trust (MFT). MFT will raise contracts with the employing

organisations of members of the trial team, which will detail the payment schedules to reimburse costs associated with working on the trial.

16. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture to answer the research question. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the REC and Competent Authority within 90 days, or 15 days if the trial is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial will be provided to the REC and Regulatory Authority within one year of the end of the trial. An end of trial report will also be issued to the funders at the end of funding.

17. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the trial database by the CTU together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with practices to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The Sponsor is responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 15 years following close of trial.

18. SATELLITE STUDIES

It is recognised, that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the Project Management Group. REC approval will be sought for any new proposal, if appropriate.

19. AUTHORSHIP PUBLICATION

At a minimum this trial will publish its final report in the funder's journal. We will endeavour to publish additional papers in high impact peer-reviewed medical/scientific journals. To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the trial by publication of newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final Newsletter to all involved in the trial.

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APPENDICES

Appendix 1: Trial Flow Diagram

Appendix 2: Qualitative study protocol

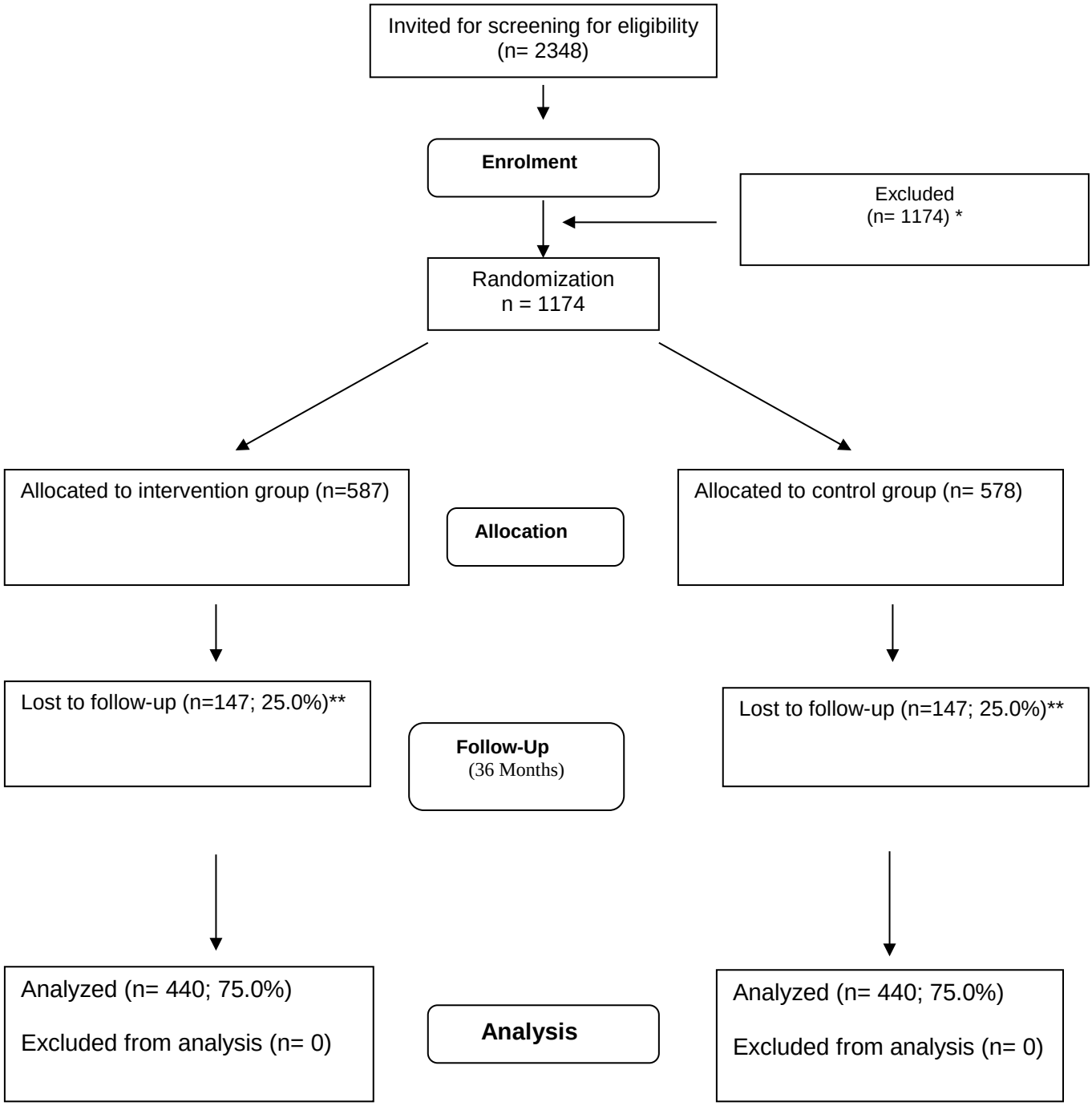
Appendix 3: Scottish sub-protocol

Appendix 4: SAE Flowchart

Appendix 1 Trial Flow Diagram

*based on 50% consent rate of the IQuaD trial

** based on 25% attrition rate over 3 years



Appendix 2: Qualitative element

Objectives

The qualitative investigation will be based on semi-structured interviews with patients aged 50 years of age or older and GDPs. A semi-structured interview approach is selected due to its flexible and interactive nature, which is useful to understand decision-making process and the shaping of individual beliefs. The objectives are to investigate GDPs' practices of and beliefs about prescribing 5000ppm fluoride toothpaste and patients' beliefs and experience of being prescribed 5000ppm fluoride toothpaste and perceived impacts on their oral health related behaviours. Furthermore, the qualitative element will also ask for GDPs' and patients' feedback concerning the design of the trial for subsequent evaluation of the project. The interviews with GDPs will explore when and how they decide to prescribe 5000ppm toothpaste and their perceived benefits of it. Furthermore, the ways in which their beliefs are shaped will also be investigated to understand how GDPs come to hold certain beliefs and how these beliefs affect their practices. Patients' views about being prescribed 5000ppm toothpaste will also be explored, particularly the ways in which the prescription affects their everyday life, routines and beliefs. GDPs and patients will also be consulted about their experience in taking part in the trial, including their views about the topic, the reason they agreed to participate in the study and what can be improved. This provides a real-time and continuous evaluation of the research design, which can be used to cross examine the validity and reliability of the trial.

Recruitment

NHS dental patients, 50 years of age or older, attending the GDP who are considered to be at high risk of developing caries. GDPs will be recruited from up to 60 practices through the existing network. Consent to be interviewed from GDPs and patients will be acquired when they are recruited for the trial. Participants will be asked if they are willing to be contacted for interviews whilst consenting to the trial. A qualitative researcher will be given the contact details of participants who consented to be interviewed and arrange telephone interviews based on participants' preference.

Data collection

Data collection will start with GDPs immediately after their consent but it will only commence four weeks after patient's consent to the study. This is to allow time for patients in the intervention groups to get used to using 5000ppm toothpaste so that they have sufficient experience to answer questions in the interviews. The interviews will be conversational and non-leading. Although an interview topic guide will be used to remind the interviewer the topics to be covered, it is expected that the conversation will follow the flow of the discussion and probing questions will be asked to tease out in-depth information (Bryman 2012). We estimate that interviews will take approximately 45-60 minutes but the length of each interview will be guided by the conversation flow. Data collection will continue until theoretical data saturation is reached.

Data management and analysis

All interviews will be audio-recorded with consent from participants and transcribed verbatim. Transcripts will be imported to qualitative analysis software (NVivo) for data management and explored using thematic analysis. The researcher will read and re-read the data to familiarise herself with the emerging ideas. Codes will then be generated in a systematic fashion across the entire data set. These codes will be collated into potential themes which will then be reviewed and refined (Braun and Clarke 2006).

Confidentiality and anonymity

Audio recording of interviews and transcripts will be either encrypted or password protected. These will be kept on the University of Manchester's secure IT service. Participants will be given a codename in the data analysis where all identifiable information will be removed.

Once the study concluded, all recordings, transcripts and documents related to this project will be stored securely at the University of Manchester for 5 years following publication of the study.

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Appendix 3: Scottish sub-protocol

6.1 Collection of Clinical Outcome Measures (Scotland only)

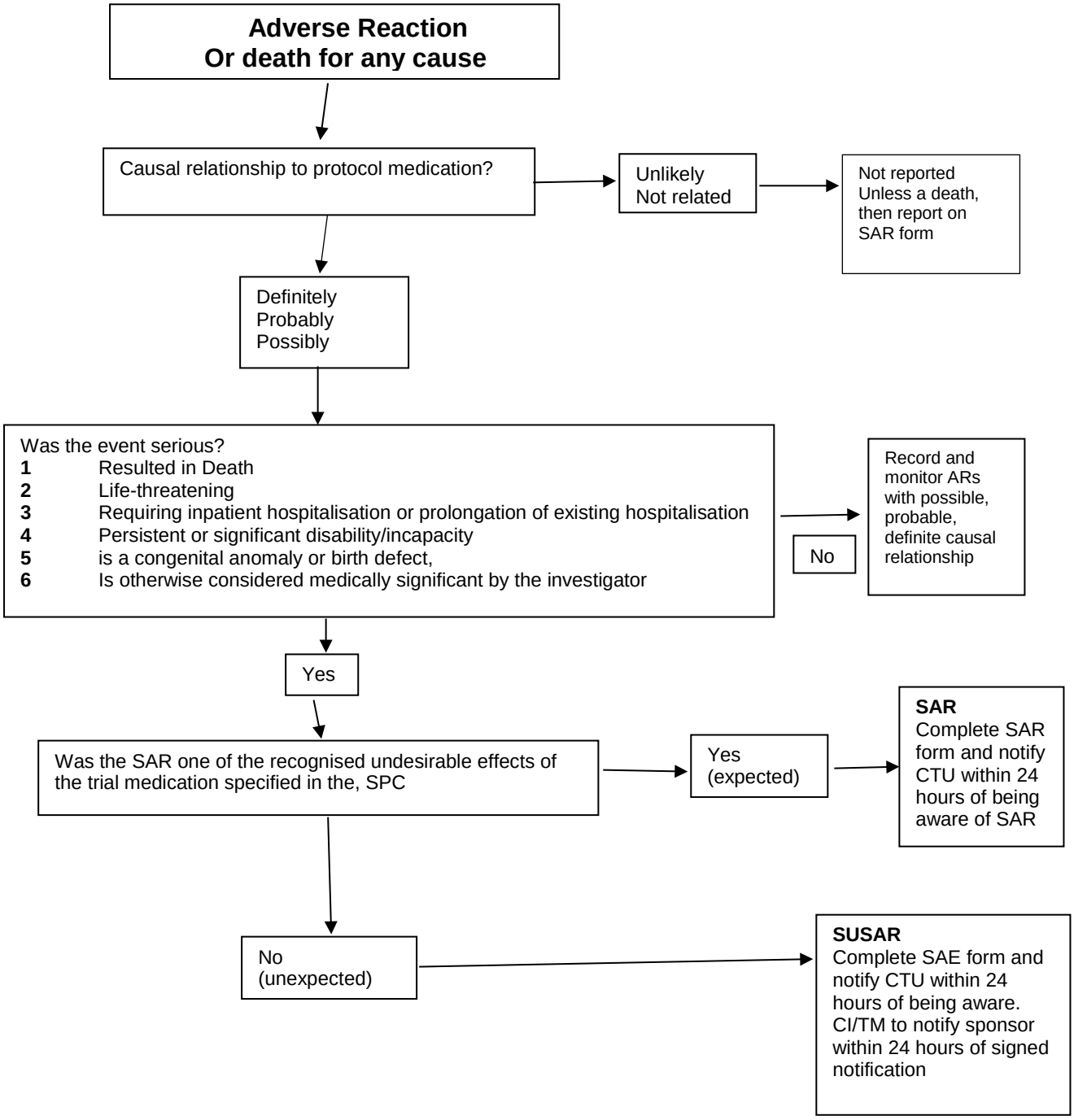
All clinical outcomes will be assessed at baseline and three years by trained examiners who are blinded to allocation. Training will be provided by an expert in caries assessment and the use of criteria in caries clinical trials.

The independent examiner will first duplicate the clinical data collection as recorded by the GDP (the condition of coronal and root surfaces).

A detailed caries measurement will be made using the validated International Caries Detection and Assessment System (ICDAS) for coronal caries. The ICDAS criteria measure both early and more advanced stages of caries. For early caries, ICDAS measures the surface changes and potential histological depth of carious lesions by relying on surface characteristics related to the optical properties of sound and demineralised enamel prior to cavitation. The primary requirement for applying the ICDAS system is the examination of clean and dry teeth aided by a ball-ended explorer that is used to remove any remaining plaque and debris and to check for surface contour, minor cavitation or sealants. All surfaces of all teeth will be examined and the caries status recorded.

Periodontal Gingival inflammation as bleeding will be measured according to the Gingival Index of Loe by running a UNC periodontal probe circumferentially around each tooth just within the gingival sulcus or pocket. After 30 seconds, bleeding will be recorded as being present or absent on the buccal and lingual surfaces.

Appendix 4: Flow Chart of assessing and notification of Adverse Reactions and Deaths



AR: Adverse reaction
SAE: Serious adverse event
SAR: Serious adverse reaction
SPC: Summary of product characteristics
SUSAR: Suspected unexpected serious adverse reaction