# InteRventions to rEduce inequaliTies in the Uptake of Routine deNtal care: Main Trial

**RETURN Main Trial Protocol**
**V6.0 14/12/2022**

**Trial Sponsor(s):**

University of Liverpool
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Liverpool
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**ISRCTN**: 84666712

**Research Ethics Ref:** 21/LO/0059

**Sponsor Ref:** UoL001595

**Funder Ref**: RP-PG-0616-20004

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# Protocol Approval

I, the undersigned, hereby approve this clinical trial protocol:

**Authorised by Chief Investigator:**

**Signature:** Rebecca Harris E7B9C32DA46542A... **Date:** 12/15/2022

**Professor Rebecca Harris**

*Dean of the Institute of Population Health Sciences*

*Professor of Dental Public Health at the University of Liverpool*

*Hon. Consultant in Dental Public Health, Liverpool University Hospitals NHS Foundation Trust*

***N.B.** due to commencement of remote working as a result of the COVID-19 pandemic, protocol approvals have been provided via email instead of wet-ink signature. Copies of these approval emails are available upon request.*

# Protocol Approval

I, the undersigned, hereby approve this clinical trial protocol:

**Authorised on behalf of Sponsor:**

**Signature:** DocuSigned by: Karen Wilding E0AD3C9FD9A84DE... **Date:** 11 January 2023

**Miss Karen Wilding**
*Senior Clinical Research Governance Manager*
*Clinical Directorate*
*Faculty of Health and Life Sciences*
*University of Liverpool*

***N.B.*** *due to commencement of remote working as a result of the COVID-19 pandemic, protocol approvals have been provided via email instead of wet-ink signature. Copies of these approval emails are available upon request.*

# Protocol Approval

I, the undersigned, hereby approve this clinical trial protocol:

**Authorised on behalf of the Lead Statistician:**

**Signature:** DocuSigned by: Girvan Burnside A3396A934F6C49B... **Date:** 12/19/2022

**Dr Girvan Burnside**

*Senior Lecturer in Biostatistics,*
*Liverpool Clinical Trials Centre,*
*University of Liverpool*

***N.B.** due to commencement of remote working as a result of the COVID-19 pandemic, protocol approvals have been provided via email instead of wet-ink signature. Copies of these approval emails are available upon request.*

**General Information**

This document describes the RETURN Main Trial including detailed information about procedures and recruitment. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial. Problems relating to this trial should be referred to the CI, Professor Rebecca Harris.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a trial process cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in Section 14.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

| **Sponsor:** | **Trial Management, Monitoring and Analysis:** |
|---|---|
| The University of Liverpool Clinical Directorate<br>Thompson Yates Building<br>The Quadrangle, Brownlow Hill,<br>Liverpool<br>L3 5RB<br><br>Tel: 0151 795 1048<br>Email: sponsor@liverpool.ac.uk | Department of Public Health, Policy and Systems<br>University of Liverpool<br>Whelan Building, 2nd Floor<br>Brownlow Street<br>Liverpool<br>L69 3GQ<br><br>Email: returntr@liverpool.ac.uk or robyn.maitland@liverpool.ac.uk |
| **Health Economics:** | **Qualitative Interviews and Central Follow Up Team:** |
| University of Leeds<br>Leeds<br>LS2 9JT<br><br>Lead by:<br>Claire Hulme<br>Professor of Health Economics<br>Health Economics Group<br>Institute of Health Research<br>University of Exeter Medical School<br>South Cloisters<br>St Luke's Campus<br>Exeter<br>EX1 2LU<br>Tel: 01392 72 2902<br><br>Email: C.T.Hulme@exeter.ac.uk | Department of Public Health, Policy and Systems<br>University of Liverpool<br>Whelan Building, 2nd Floor<br>Brownlow Street<br>Liverpool<br>L69 3GQ<br><br>Email: v.lowers@liverpool.ac.uk |

## Contact Details: Individuals

| Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor: | Chief Investigator (CI): |
|---|---|
| Karen Wilding<br>Senior Clinical Research Governance Manager<br>The University of Liverpool Clinical Directorate<br>Thompson Yates Building<br>The Quadrangle, Brownlow Hill,<br>Liverpool<br>L3 5RB<br>Tel: 00 44 (0) 7717 863747<br>Email: sponsor@liverpool.ac.uk | Professor Rebecca Harris<br>Professor of Dental Public Health at the University of Liverpool<br>Whelan Building, 2nd Floor<br>Brownlow Street<br>Liverpool<br>L69 3GQ<br>Email: harrisrv@liverpool.ac.uk |

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

| Medical Expert who will Advise on Protocol Related Clinical Queries: | Medical Expert who will Evaluate SAE Reports: |
|---|---|
| Professor Jan Clarkson<br>Co-Director DHSRU; Director, Effective Dental Practice Programme and Associate Dean for Research<br>Division of Oral Health Sciences<br>Dental Hospital & School<br>Park Place<br>Dundee<br>DD1 4HR<br>Tel: +44 (0) 1382740 990<br>Email: j.e.clarkson@dundee.ac.uk | Professor Jan Clarkson<br>Co-Director DHSRU; Director, Effective Dental Practice Programme and Associate Dean for Research<br>Division of Oral Health Sciences<br>Dental Hospital & School<br>Park Place<br>Dundee<br>DD1 4HR<br>Tel: +44 (0) 1382740 990<br>Email: j.e.clarkson@dundee.ac.uk<br><br>Professor Rebecca Harris<br>Department of Public Health, Policy & Systems<br>University of Liverpool<br>2nd Floor Whelan Building<br>Liverpool L69 3GB<br>Tel +44 (0)151 795 5334<br>Mobile: 07783 821511<br>Email: harrisrv@liverpool.ac.uk |

**Additional Contacts:**

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

| Contact | Document Title |
|---|---|
| Programme Management Group (PMG)<br>Programme Steering Committee (PSC)<br>Trial Management Group (TMG) | RETURN Trial Oversight Committee Membership |
| Principal Investigators | RETURN Participating Centres |

# 1 Table of Contents

# 2 Glossary

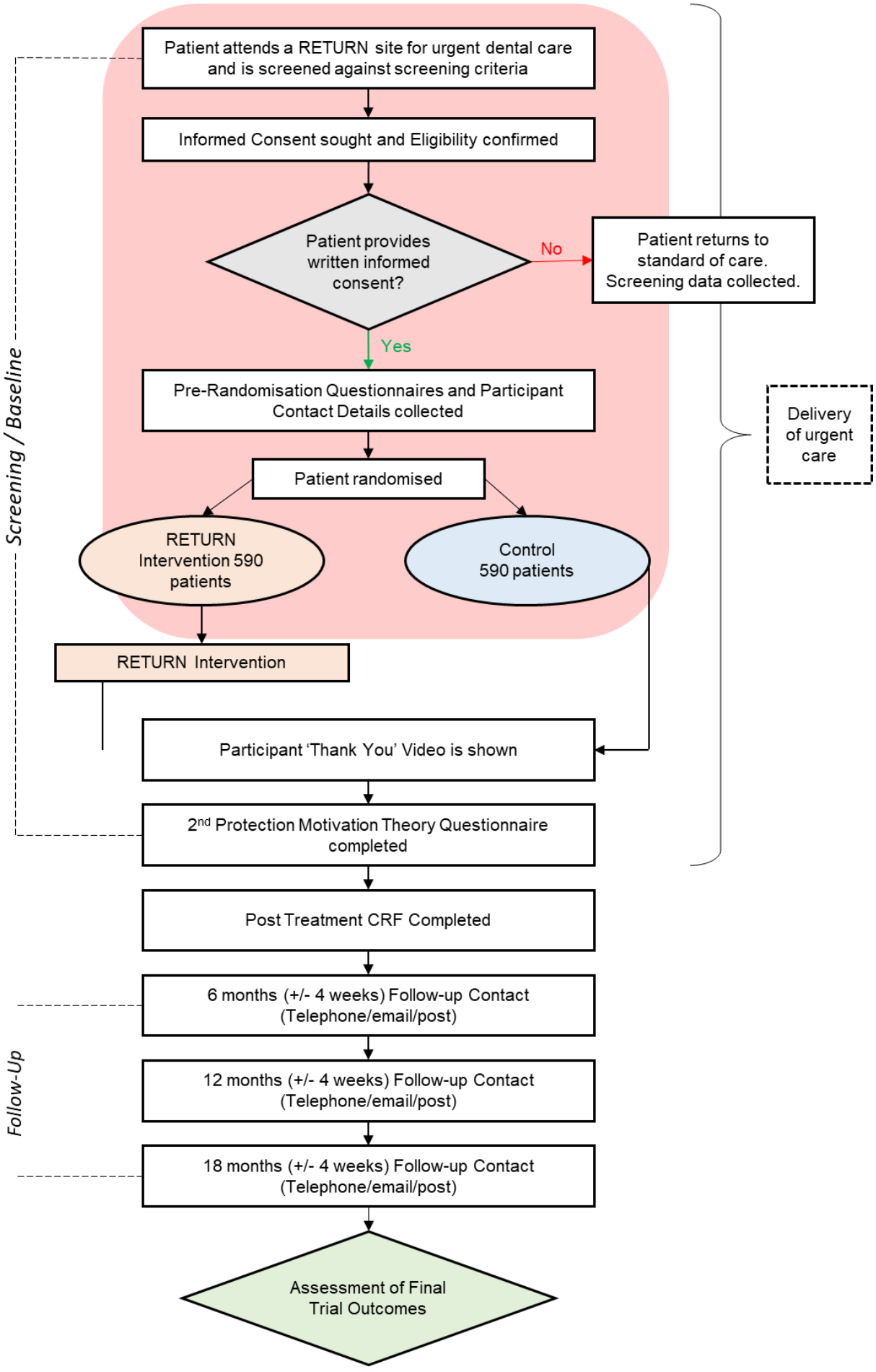
| | |
|---|---|
| AE | Adverse Event |
| A&E | Accident & Emergency department |
| BSA | Business Services Authority |
| CI | Chief Investigator |
| CRF | Case Report Form |
| ECRF | Electronic Case Report Form |
| GP | General Practitioner |
| HEAP | Health Economics Analysis Plan |
| HES | Hospital Episode Statistics |
| HRA | Health Research Authority |
| IMD | Index of Multiple Deprivation |
| LCTC | Liverpool Clinical Trials Centre |
| NHS | National Health Service |
| NIHR CRN | National Institute for Health Research Clinical Research Network |
| NRES | National Research Ethics Service |
| OHIP | Oral Health Impact Profile |
| PI | Principal Investigator |
| PHPS | (department of) Public Health, Policy and Systems |
| PMT | Programme Management Team |
| PROM | Patient Reported Outcome Measure |
| PSC | Programme Steering Committee |
| QALY | Quality Adjusted Life Years |
| QOL | Quality of Life |
| R&D | Research & Development |
| REC | Research Ethics Committee |
| RN | Research Nurse (Registered) |
| RSI | Reference Safety Information |
| RSO | Research Support Office |
| SAE | Serious Adverse Event |
| SES | Social Economic Status |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| TC | Trial Coordinator |
| TM | Trial Manager (part of the PHPS department) |

# 3 Protocol Overview

| | |
|---|---|
| **Full Title:** | InteRventions to rEduce inequaliTies in the Uptake of Routine deNtal care |
| **Acronym:** | RETURN |
| **Phase:** | III |
| **Target Population:** | This trial will recruit adults aged 18 and over who have the capacity to consent, require urgent dental care within Merseyside and Cheshire and only attend dental services when they have an emergency. |
| **Sample size:** | 1180 |
| **Inclusion Criteria:** | 1. Adults (aged 18 years or over) seeking urgent dental care.<br>2. Has not visited an NHS or Private dentist for a non-emergency appointment (i.e. when not in pain or symptomatic) for 2 years or more, and do not have a dentist who they visit regularly for routine care.<br>3. Able to provide either a telephone number, email or postal address to allow follow up.<br>4. Has provided written consent.<br>5. Adequate understanding of spoken and written English.<br>6. Responsible for making their own dental appointments i.e. not done by a carer. |
| **Exclusion Criteria:** | 1. Have previously been enrolled in the RETURN feasibility or main trial.<br>2. Lives with, or related to, a participant in the RETURN feasibility or main trial.<br>**Note:** Patients who go on to have planned care with undergraduate students will not be excluded, although the route patients' take to planned care will be reported. |
| **Trial Centres and Distribution:** | Dental practices with in-hours urgent dental care contracts, out of hours dental practices and Liverpool Dental Hospital |
| **Participant Trial Duration:** | Up to 19 months per participant |
| **Trial Duration:** | 31 months |
| **Intervention:** | **Intervention:** A specifically developed opportunistic psychological intervention that has been produced by the RETURN programme for use in this trial |
| | **Control:** Standard care per site |

| **Objectives:** | |
|---|---|
| **Primary:** | 1. To identify whether there is a difference between intervention and control groups in rates of attendance at a dental practice (as measured by BSA data) for a planned care appointment within 12 months,.<br><br>2. To identify whether there is a difference in oral health quality of life (as measured by the final value of OHIP, adjusting for the baseline value). 12 months after randomisation<br><br>Refer to Section 9 for further details on endpoint/outcome measures |
| **Secondary:** | 1. To identify whether the behavioural intervention has different effects across the socio-economic gradient.<br><br>2. To identify the psychological factors which mediate any intervention effect.<br><br>3. To identify whether there is a difference between intervention and control groups in self-reported rates of attendance at a dental practice or Dental Hospital and/or attempts to make an appointment to see a dentist for planned dental care during the follow-up period.<br><br>4. To identify whether there is a difference between intervention and control groups in rates of attendance at a dental practice (as measured by BSA data) or Dental Hospital for a planned care appointment within 18 months.<br><br>5. To identify whether there is a difference between intervention and control groups in oral health quality of life at 6 and 18 months.<br><br>6. To identify whether there is a difference between intervention and control groups in halitosis and bad taste as indicators of dental infection (self-reported) at 6, 12 and 18 months<br><br>7. To identify whether there is a difference between intervention and control groups in the clinical dental treatment received by participants at 6, 12 and 18 months.<br><br>8. To identify whether there is a difference between intervention and control groups in self-reported rates of attendance for urgent dental care at dental practices, A & E, GP practices and urgent dental care services including Dental Hospital at 6, 12 and 18 months.<br><br>9. To identify whether there is a difference between intervention and control groups in rates of antibiotics or analgesics for dental problems prescribed by a Dentist, GP, A & E department or walk-in centre, at 6, 12 and 18 months<br><br>10. To monitor any change in dental anxiety after receiving the intervention.<br><br>11. To estimate the cost effectiveness of the intervention compared with usual care at 12 and 18 months. |

## 3.1 Schematic of Trial Design



# 4 Roles and Responsibilities

## 4.1 Sponsor

The Sponsor is the University of Liverpool and is legally responsible for the trial. They will formally delegate specific Sponsoring roles to the CI and Clinical Trials Unit. The Sponsor will ensure that clear agreements are reached, documented and carried out, respecting the dignity, rights, safety and wellbeing of participants and the relationship with healthcare professionals. This will provide for proper design, management, initiation, conduct, monitoring, data collection, data analysis, data protection, financing and reporting of this trial, meeting appropriate scientific, legal and regulatory standards

## 4.2 Funder

The funder of this trial is the National Institute for Health Research who is providing financial funding through the Programme Grants for Applied Research. The funder will ensure there is proper use of the funds they have allocated to provide value for money. The funder assures the quality of the trial, taking the lead in establishing that the research proposal is worthwhile, of high scientific quality, has an appropriate research infrastructure with expert clinical trial management, has the capacity to comply with the principles of GCP and represents good value for money.

## 4.3 Chief Investigator

Professor Rebecca Harris is the CI for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the trial team.

## 4.4 Principal Investigators (PI's)

In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, and adherence to trial protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

## 4.5 Trials Unit (LCTC)

LCTC at the University of Liverpool in collaboration with the CI, will have responsibility for data management, randomisation, statistical analysis and participating site coordination.

## 4.6 Department of Public Health Policy and Systems (Central Research Team)

The RETURN team at the Department of Public Health Policy and Systems at the University of Liverpool will have management responsibility for trial related activities including (but not limited to) trial planning, budget administration, training and site set up, ongoing support and communication with participating sites, follow up of trial participants, and embedded qualitative work. Trial management/trial master file management and safety reporting will also be the responsibility of the PHPS.

## 4.7 Oversight Committees

The RETURN trial is subject to oversight from the following committees:

### 4.7.1 Programme Management Group (PMG)

The RETURN main trial is positioned in a wider piece of work involving a qualitative work package and community engagement work. The PMG was particularly involved in the developmental stage of the intervention, and will continue to meet periodically (at least once a year) during the conduct of the trial, follow up and reporting, to enable discussion with co-investigators such as psychologists and qualitative researchers who are not involved with day to day planning of trial management activities.

### 4.1.1 **Trial Management Group (TMG)**

A Trial Management Group (TMG) will be formed comprising the CI, other lead investigators involved in the trial (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly or as required.

### 4.1.2 **Programme Steering Committee (PSC)**

The PSC will monitor the programme e.g. against milestones; and to advise on methodological aspects and implementation issues. The PSC will include:

- an independent chair
- an independent psychological expert
- an independent economic expert
- a biostatistician
- lead members of the TMG

The PSC will meet bi-annually, or at points as advised by the PSC. Refer to the PSC terms of reference and trial oversight committee membership document for further details.

Given that adverse effects of the intervention are judged to be limited, the PSC have agreed that an Independent Data and Safety Monitoring Committee (IDSMC) will not be required for the trial. Safety will be reviewed by the PSC.

## Protocol Contributors

| Name | Affiliations | Contribution to protocol |
|---|---|---|
| Rebecca Harris | Department of Public Health, Policy & Systems, University of Liverpool | Conceived the trial, led the design and writing of this protocol, clinical and scientific arrangements, governance arrangements trial design and conduct |
| Victoria Lowers | Department of Public Health, Policy & Systems, University of Liverpool | Protocol development, governance arrangements and trial conduct |
| Marieke Van Der Zande | Department of Public Health, Policy & Systems, University of Liverpool | Background and qualitative methods |
| Claire Hulme | University of Exeter | Health Economics, Protocol development |
| Nahel Yaziji | Health Economics Research Assistant, University of Leeds | Health Economics, Protocol Development |
| Jan Clarkson | University of Dundee | Protocol development, and trial conduct |
| Emma Bedson | LCTC, University of Liverpool | Protocol development, governance arrangements and trial conduct |
| Grace Thomas | LCTC, University of Liverpool | Protocol development, governance arrangements and trial conduct |

| | | |
|---|---|---|
| Sean Gaines | LCTC, University of Liverpool | Protocol development, governance arrangements and trial conduct |
| Ashley Best | LCTC, University of Liverpool | Statistical arrangements, trial design and conduct |
| Girvan Burnside | Department of Health Data Science, University of Liverpool | Protocol development, statistical arrangements, trial design and conduct. |
| Robyn Kirby (formally Maitland) | LCTC, University of Liverpool (02/2021-07/2022) and Department of Public Health, Policy & Systems, University of Liverpool (from 07/2022 onwards) | Protocol development, governance arrangements and trial conduct |

# 5 INTRODUCTION

## Background

Dental diseases are among the most common chronic diseases worldwide, and the costs of these diseases amount to an estimated $356.80 billion in treatment expenditures and $187.61 billion in productivity losses[1]. Oral health is characterised by a clear social gradient similar to that found in general health, with people from more deprived socioeconomic backgrounds experiencing worse oral health[2-4]. A large body of evidence shows that dental attendance is linked to better oral health[5-7]. In addition, patients with regular dental attendance perceive their oral health as having a greater positive impact on their quality of life[8]. Dental attendance is known to be lower among people from lower socioeconomic backgrounds[6, 7]. Moreover, several studies have shown that the widely known socioeconomic inequalities in oral health are to a considerable extent mediated by dental attendance[9-11].

Dental attendance is multi-faceted and can vary during the life course. Earlier studies have adopted a distinction between regular and irregular attenders[8], often based on dental attendance over the preceding 12 months. More recent studies focus on long-term patterns in dental attendance[6, 7, 12]. These studies show that dental attendance varies during the life-course, and that a minority of patients maintain dental attendance consistently throughout their lives, and a small minority never visit a dentist. Long-term consistent dental attendance is associated with better oral health compared to patients who do not visit a dentist at present but used to do so, and patients who never regularly attended dental care services [6, 7, 12]. Patients who attend the dentist regularly mostly do so for planned visits, for example check-ups. These have been shown to be more beneficial for oral health than problem-based visits. The benefit of dental attendance for check-ups is not related to a specific recall time interval for all patients[13]. Recall intervals of between 3 months and 24 months may all be appropriate for sub-groups of patients, and no one interval fits all patients. In order to include all intervals that may be classed as continuing dental attendance, we define 'dental attendance' as having visited a dentist in the past 24 months for a planned care appointment.

People with more irregular attendance patterns often wait until there is a problem. Examples of such problems are toothache and swelling. Such acute dental problems lead to pain, often over a period of several weeks[14], and may impact on health-related quality of life[14, 15]. Patients who experience acute dental problems often seek care in emergency dental services, or in general and emergency medical services. Such emergency service visits often result in treatment with an antibiotic prescription[16, 17]. This in turn may contribute to antimicrobial resistance, a pivotal public health concern[18, 19]. In addition, serious consequences can result from a dental abscess developing into sepsis, which then may require hospitalisation, resulting in high costs for the NHS[20]. In short, attendance when there is an acute dental problem may lead to high costs, and the treatments given for acute dental problems are often temporary and of limited effectiveness [17, 21].

## Rationale

A brief psychological intervention (the RETURN intervention) has been developed to be delivered to adults attending dental services for emergency care. The intervention has been developed using extensive qualitative work and with patient and public involvement to ensure that its format is especially relevant for those from disadvantaged backgrounds. In order to promote planned dental visiting, and through this to improve oral health, and reduce impacts of oral disease such as toothache and use of antibiotics for dental problems, the psychological intervention uses multiple behaviour change techniques. The delivery of the RETURN intervention has been previously tested in a feasibility study.

The RETURN trial will recruit 1,180 urgent dental care users to a randomised controlled trial across three types of urgent care setting: a Dental Hospital, in-hours urgent care and out-of-hours urgent care, over a period of 12 months, following those patients up for a period of 18 months.

# Risk and Benefits

### 5.1.1 **Potential Risks**

There are no known risks of the intervention, to either the trial participants, or the trial research teams, which involves giving information and helping plan for appointments and dental visits.

### 5.1.2 **Potential Benefits**

The RETURN intervention may help with barriers that some people have to going to the dentist, by attending regular dental appointments, the impact is reduced on urgent care and subsequent costs to the NHS.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment, maintained in the Trial Master File.

### 5.1.3 **Impact of COVID-19**

All participants recruited into the trial will be those attending NHS urgent dental services. This is where the intervention will be delivered, and the follow-up of participants takes place remotely (telephone, e mail or by post). Urgent dental services have continued to function throughout the period of disruption due to the pandemic – including during the first wave in March 2020, when routine dental services were closed between March and 8th June 2020.

Routine dental services have resumed functioning from June 2020 and have continued to do so throughout the second wave of the pandemic - including during the second lockdown period. This is because of guidance concerning the risk of providing routine dentistry including fillings which are Aerosol Generating Procedures (AGP), have been re-evaluated as the knowledge about risks and mitigation (suction/ventilation/rubber dam/leaving the surgery empty for a period afterwards) has grown. Initial recommendations were for surgeries to be left empty for 60 minutes after an AGP, but more recent guidance has brought in a more nuanced approach where this can be shortened if the ventilation is appropriate.

Routine dental practices have now resumed providing a full range of care, even in the midst of the second wave. There is currently some backlog in routine care as practitioners are catching up after a period of practice closure. On the other hand, commissioners have significantly lightened the target driven system of remuneration for dental practices which drives them to want to take on certain types of work, and so dentists may be actually keener to take on new patients and work in a slightly different way as a consequence.

The COVID-19 pandemic does not impact the likelihood of successful recruitment, delivery of the intervention, or the follow-up. The only risk would be as to whether patients would find it more difficult to access routine dental services than before. Arguably this actually strengthens the case for the need of the intervention which has been designed – in that it equips patients who are from more disadvantaged backgrounds, the skills, information and confidence to access services. The objective of the intervention is to promote the uptake of regular dental care and we believe that when the trial is scheduled to start, there will be sufficient availability of routine dental services for patients.

# Objectives

### 5.1.4 **Primary Objectives**

1. To identify whether there is a difference, between intervention and control groups in rates of attendance at a dental practice (as measured by BSA data) for a planned care appointment within 12 months.

2. To identify whether there is a difference in oral health quality of life (as measured by the final value of OHIP, adjusting for the baseline value) 12 months after randomisation.

### 5.1.5 **Secondary Objective(s)**

1. To identify whether the behavioural intervention has different effects across the socio-economic gradient.

2. To identify the psychological factors which mediate any intervention effect.

3. To identify whether there is a difference between intervention and control groups in self-reported rates of attendance at a dental practice or dental hospital and/or attempts to make an appointment to see a dentist for planned dental care during the follow-up period.

4. To identify whether there is a difference between intervention and control groups in rates of attendance at a dental practice (as measured by BSA data) or dental hospital for a planned care appointment within 18 months,

5. To identify whether there is a difference between intervention and control groups in oral health quality of life at 6 and 18 months.

6. To identify whether there is a difference between intervention and control groups in halitosis and bad taste as indicators of dental infection (self-reported) at 6, 12 and 18 months

7. To identify whether there is a difference between intervention and control groups in the clinical treatment received by participants at 6,12 and 18 months.

8. To identify whether there is a difference between intervention and control groups in self-reported rates of attendance for urgent dental care at dental practices, A & E, GP practices, and urgent dental care services including dental hospital at 6, 12 and 18 months.

9. To identify whether there is a difference between intervention and control groups in rates of antibiotics or analgesics for dental problems prescribed by a dentist, GP, Accident and Emergency department or walk-in centre at 6,12 and 18 months.

10. To monitor any change in dental anxiety after receiving the intervention.

11. To estimate the cost effectiveness of the intervention compared with usual care at 12 and 18 months.

# 6 TRIAL DESIGN

The RETURN main trial is a randomised controlled open trial to develop and test a way to improve the routine use of dental services by deprived populations, by delivering a psychological intervention personalised to participants to address the significant barriers to attending regular dental appointments and to encourage behavioural changes.

The trial aims to assess the effectiveness and cost-effectiveness of an opportunistic psychological intervention for urgent dental care service users and to explore whether the psychological intervention has different effects across the socio-economic gradient.

The RETURN main trial will recruit 1,180 urgent dental care users over twelve months from three site types: a Dental Hospital, out-of-hours urgent care practices and in-hours urgent care practices. Participants for the main trial will be followed up at 6, 12 and 18 months after randomisation.

## Blinding

This is an open label trial with no blinding requirements. Due to the nature of the RETURN intervention, blinded allocations cannot be maintained at RETURN sites. In addition, due to the nature of follow-up, blinded allocations cannot be maintained for researchers completing the follow-up.

## Trial Setting

Urgent dental care across is provided by Liverpool Dental Hospital and in hours general dental practices (GDP), through locally commissioned urgent care contracts, and an out of hours dental service. These provide the bulk of emergency care for patients who do not have their own dentist. Some other NHS dental practices provide urgent care for patients who do not have their own dentist, but there may be relatively few numbers of such patients in these practices. Within this area recruitment will take place where urgent dental care delivery occurs as standard practice, therefore there will be 3 site types:

- Dental Hospital
- Out of hours dental care NHS general dental practices
- In hours urgent dental care NHS general dental practices

### 6.1.1 **Selection of Participating Sites**

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in a separate document ‘RETURN Main Trial Site Suitability Assessment’ maintained in the Trial Master File (TMF).

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the RETURN main trial and will be opened to recruitment upon successful completion of all global (e.g. Research Ethics Committee – REC) and trial-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC.

Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist, which is maintained in the TMF and must be fully completed prior to opening sites to recruitment.

### 6.1.2 **Selection of Principal Investigators**

For each site that fulfils the trial-specific criteria, a PI will be identified. The PI will be an individual considered to be the most appropriate by the Practice Owner, and who is prepared to complete training and conduct

trial-specific procedures. Written agreement to conduct research as such will be obtained prior to the initiation of the site.

# 7 ELIGIBILITY CRITERIA

The RETURN trial aims to recruit 1180 participants based on sample size calculations described in Section 12.2. All participants must provide written, informed consent before any trial procedures occur (see Section 10.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

## Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

1. Adults (aged 18 years or over) seeking urgent dental care.
2. Has not visited an NHS or Private dentist for a non-emergency appointment (i.e. when not in pain or symptomatic) for 2 years or more, and do not have a dentist who they visit regularly for routine care
3. Able to provide either a telephone number, email or postal address to allow follow up.
4. Has provided written consent.
5. Adequate understanding of spoken and written English.
6. Responsible for making their own dental appointments i.e. not done by a carer.

## Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from trial participation:

1. Have previously been enrolled in the RETURN feasibility or main trial.
2. Lives with, or related to, a participant in the RETURN feasibility or main trial.

**Note**: Patients who go on to have planned care with undergraduate students will not be excluded, although the route that patients' take to planned care will be reported.

## Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials during their participation in the RETURN Main Trial.

Where recruitment into another trial is considered to be appropriate, and without having any detrimental effect on the RETURN Main Trial, this must first be discussed with the LCTC who will contact the CI (Professor Rebecca Harris).

# 8 TRIAL INTERVENTION

## Introduction

Participants will be randomised in a ratio of 1:1 to either the RETURN intervention or control.

**RETURN intervention:** An opportunistic psychological intervention that has been developed by the RETURN programme for use in this trial. Those who are randomised to the RETURN intervention will return to standard care once the RETURN intervention has been completed.

**Control:** Participants will receive the usual care that is provided by the site they were recruited at.

## RETURN Intervention Group

Participants randomised to the RETURN intervention will receive a booklet pack providing information about dental visiting barriers. Each participant will be given the opportunity to view online video clips and materials on a tablet PC which supplement the booklet pack. Each intervention participant will identify relevant reasons why they do not currently use planned dental care and will receive information about these. This will be guided by a trained dental team member or researcher. The booklet pack will contain resources for participants to use such as a credit card sized information card, which the participant can give to their employer, and which advises that further dental care appointments are needed. The booklet pack contains a set of resources to help participants when they attend a routine dental appointment, such as information on relaxation exercises which they might use when waiting for their dental appointment.

While in the dental setting, using the booklet material, participants will make a goal regarding attending for a planned dental appointment, and at least one action plan that will help them overcome their barriers to dental visiting. These will be photographed by the dental team member or researcher on the Tablet PC and uploaded on to the trial database to facilitate a follow-up text which will be sent within 2 weeks of the participant receiving the intervention.

Participants will be shown a short, animated video thanking them for participating in the trial and telling them what to expect in subsequent follow-up contacts in 6, 12- and 18-months' time. Participants will view this video while in the dental setting just before completing the final questionnaire which is a repeat of the Protection Motivation theory questions

Participants will receive a follow up text with an online link to the material and videos which will be accessed via a restricted access web portal, and with a supportive message around the participant's action plan (s) recorded. This will be managed by the central follow up research team.

## Control Group

For participants randomised to the control, they will receive standard care from the site where they were recruited. Participants will be shown a short, animated video thanking them for participating in the trial and telling them what to expect in subsequent follow-up contacts in 6, 12- and 18-months' time. Participants will view this video while in the dental setting just before completing the final questionnaire which is a repeat of the Protection Motivation theory questions.

# 9 OUTCOMES

## Primary Outcomes

Primary outcome 1: Attendance at a dental practice for a planned care appointment within 12 months, collected from BSA data.

Primary outcome 2: Self-reported oral health quality of life, measured by the value at 12 months of the summary score OHIP-14

## Secondary Outcomes

Secondary outcome 1: Attendance at a dental practice or dental hospital for a planned care appointment, self-reported at 6, 12 and 18 months

Secondary outcome 2: Attendance at a dental practice for a planned care appointment within 18 months, collected from BSA data

Secondary outcome 3: Attempts to make an appointment to see a dentist for planned dental care as measured by patient self-report at 6,12 and 18 months

Secondary outcome 4: Self-reported oral health quality of life, measured by the final value of the summary score of OHIP-14 adjusting for baseline value, at 6 and 18 months.

Secondary outcome 5: Urgent attendance for dental care at dental practice, A&E, GP, or dental hospital, self-reported 6,12 and 18 months

Secondary outcome 6: Halitosis and Bad taste, measured by patient self-report at 6 12 and 18 months

Secondary outcome 7: Treatment received, as measured by BSA clinical dataset, patient self-report and dental hospital audit at 6, 12 and 18 months

Secondary outcome 8: Antibiotic prescription by dentists, measured by BSA data, dental hospital audit and self-report at 6,12 and 18 months.

Secondary outcome 9: Antibiotic prescription for dental problems by a GP/A&E/walk-in-centre, measured by patient self-report at 6,12 and 18 months

Secondary outcome 10 Analgesic prescription for dental problems, measured by patient self-report at 6, 12 and 18 months

Secondary outcome 11: (safety): Dental anxiety, as measured by the Modified Dental Anxiety Scale recorded by patient self-report at 6, 12 and 18 months

Secondary outcome 12: Incremental cost-effectiveness ratio at 12 and 18 months derived from BSA data, patient self-report resource use and EQ-5D-5L at baseline, 6, 12 and 18 months

Secondary outcome 13: Attendance at a dental practice or Dental Hospital for a planned care appointment within 18 months, collected in BSA data and Dental Hospital audit

Secondary outcome 14: Self-reported beliefs to using planned dental services measured using Protection Motivation questionnaire (as a mediator)

**Table 1: Objectives, Outcome Measures, Timepoint(s) and Methods of Evaluation**

| Objectives | | Outcomes | |
|---|---|---|---|
| **Primary** | | | |
| Primary objective 1 | To identify whether there is a difference between intervention and control groups in rates of attendance for a planned care appointment at a dental practice within 12 months (as measured by NHS Business Services Authority [BSA] data). | Primary outcome 1 | Attendance at a dental practice for a planned care appointment within 12 months, collected from BSA data. |
| Primary objective 2 | To identify whether there is a difference in oral health-related quality of life 12 months after randomisation. | Primary outcome 2 | Self-reported oral health-related quality of life as measured by the value at 12 months of the summary score of the short form Oral Health Impact Profile (OHIP-14) |
| **Secondary** | | | |
| Secondary objective 1 | To identify whether the behavioural intervention has different effects across the socio-economic gradient. | Primary outcome 1 | Attendance at a dental practice for a planned care appointment within 12 months, collected from BSA data. |
| | | Primary outcome 2 | Self-reported oral health quality of life, measured by the value at 12 months of the summary score of OHIP-14 |
| | | Secondary outcome 1 | Attendance at a dental practice or Dental Hospital for a planned care appointment, self-reported at 6, 12 and 18 months |
| | | Secondary outcome 3 | Attempts to make an appointment to see a dentist for planned dental care as measured by patient self-report at 6,12 and 18 months |
| | | Secondary outcome 8 | Antibiotic prescription by dentists, measured by BSA data, Dental Hospital audit and self-report at 6,12 and 18 months |
| | | Secondary outcome 9 | Antibiotic prescription for dental problems by GP/A&E/walk-in-centre, measured by patient self-report at 6,12 and 18 months |
| | | Secondary outcome 11 | (safety): Dental anxiety, as measured by the Modified Dental Anxiety Scale recorded by patient self-report at 6,12 and 18 months |

| | | | |
|---|---|---|---|
| | | Secondary outcome 7 | Treatment received, as measured by BSA clinical dataset, patient self-report and Dental Hospital audit at 6,12 and 18 months |
| Secondary objective 2 | To identify the psychological factors which mediate any intervention effect. | Primary outcome 1 | Attendance at a dental practice for a planned care appointment within 12 months, collected from BSA data. |
| | | Primary outcome 2 | Self-reported oral health quality of life, measured by the value at 12 months of the summary score of OHIP-14 |
| | | Secondary outcome 1 | Attendance at a dental practice or Dental Hospital for a planned care appointment, self-reported at 6, 12 and 18 months |
| | | Secondary outcome 3 | Attempts to make an appointment to see a dentist for planned dental care as measured by patient self-report at 6,12 and 18 months |
| | | Secondary outcome 2 | Attendance at a dental practice for a planned care appointment within 18 months, collected from BSA data |
| | | Secondary outcome 13 | Attendance at a dental practice or Dental Hospital for a planned care appointment within 18 months, collected in BSA data and Dental Hospital audit |
| | | Secondary outcome 4 | Self-reported oral health quality of life, measured by the final value of the summary score of OHIP-14 adjusting for baseline value, at 6 and 18 months. |
| | | Secondary outcome 14 | Self-reported beliefs to using planned dental services measured using Protection Motivation questionnaire (as a mediator). |
| Secondary objective 3 | To identify whether there is a difference between intervention and control groups in self-reported rates of attendance and/or attempts to make an appointment at a dental practice or Dental Hospital for planned dental care during the follow-up period. | Secondary outcome 1 | Attendance at a dental practice or Dental Hospital for a planned care appointment, self-reported at 6, 12 and 18 months |
| | | Secondary outcome 3 | Attempts to make an appointment to see a dentist for planned dental care as measured by patient self-report at 6,12 and 18 months. |
| Secondary objective 4 | To identify whether there is a difference between intervention and control groups in rates of attendance at a dental practice (as measured by BSA data) or Dental Hospital for | Secondary outcome 2 | Attendance at a dental practice for a planned care appointment within 18 months, collected from BSA data |
| | | Secondary outcome 13 | Attendance at a dental practice or Dental Hospital for a planned care appointment within 18 months, collected in BSA data and Dental Hospital audit |

| | | | |
|---|---|---|---|
| | a planned care appointment within 18 months. | | |
| Secondary objective 5 | To identify whether there is a difference between intervention and control groups in oral health quality of life at 6 and 18 months. | Secondary outcome 4 | Self-reported oral health quality of life, measured by the final value of the summary score of OHIP-14 adjusting for baseline value, at 6 and 18 months. |
| Secondary objective 6 | To identify whether there is a difference between intervention and control groups in halitosis and bad taste as indicators of dental infection at 6, 12 and 18 months. | Secondary outcome 6 | Halitosis and Bad taste, measured by patient self-report at 6, 12 and 18 months |
| Secondary objective 7 | To identify whether there is a difference between intervention and control groups in the clinical dental treatment received at 6, 12 and 18 months. | Secondary outcome 7 | Treatment received, as measured by BSA clinical dataset, patient self-report and Dental Hospital audit at 6,12 and 18 months |
| Secondary objective 8 | To identify whether there is a difference between intervention and control groups in self-reported rates of attendance for urgent care at dental practices, A & E, GP practices and urgent dental care services including Dental Hospital at 6, 12 and 18 months. | Secondary outcome 5 | Urgent attendance for dental care at dental practices, A&E, GP practices, or Dental Hospital. Self-reported at 6,12 and 18 months |
| Secondary objective 9 | To identify whether there is a difference between intervention and control groups in rates of antibiotics or analgesics for dental problems prescribed by a dentist, GP Accident and Emergency department or walk-in centre at 6, 12 and 18 months. | Secondary outcome 8 | Antibiotic prescription by dentists, measured by BSA data, Dental Hospital audit and self-report at 6,12 and 18 months |
| | | Secondary outcome 9 | Antibiotic prescription for dental problems by GP/A&E/walk-in-centre, measured by patient self-report at 6,12 and 18 months |
| | | Secondary outcome 10 | Analgesic prescription for dental problems, measured by patient self-report at 6, 12 and 18 months. |
| Secondary objective 10 | To monitor any change in dental anxiety after receiving the intervention. | Secondary outcome 11 | (safety): Dental anxiety, as measured by the Modified Dental Anxiety Scale recorded by patient self-report at 6,12 and 18 months |
| Secondary objective 11 | To estimate the cost effectiveness of the intervention compared with usual care at 12 and 18 months. | Secondary outcome 12 | Incremental cost-effectiveness ratio at 12 and 18 months derived from BSA data, patient self-report resource use and EQ-5D-5L at baseline, 6, 12 and 18 months |

# 10 PARTICIPANT TIMELINES AND ASSESSMENTS

## Participant Identification and Screening

A banner/poster in the dental service will inform patients that a research study is taking place at the site. Patients potentially eligible to participate will be given an A5 leaflet by a trained dental team or researcher (thereafter termed RETURN trained staff) when they arrive at their appointment to explain that this study is taking place.

Patients who are 18 years old or over, who have an adequate understanding of English and who do not have their own dentist that they visit for check-ups and treatment will be classified as potentially eligible patients. A trained dental team member or researcher (thereafter termed RETURN trained staff) will routinely ask questions about the patient's age, ability to understand English and to determine whether a patient has their own dentist. A patient may be eligible to be approached to take part in the RETURN main trial if they state they do not have their own dentist and that they have not visited a dentist for a period of two years or more when they were not in pain or symptomatic, i.e. they have not attended a planned dental appointment in the last two years. They will be identified on arrival at RETURN sites and once identified they will be entered onto the RETURN screening log by RETURN trained staff and approached about RETURN if potentially eligible.

During initial discussions about RETURN, if a patient does not fulfil the eligibility criteria then the reasons for this will be recorded on the screening log. The paper-based screening log will also collect information regarding reasons for non-consent and other information used for monitoring purposes will be collected by the TC or RETURN trained staff visiting the practices. No personal identifiers will be recorded.

## Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation.. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent, they do not have to give a reason.

Following screening, consent will be sought from potentially eligible patients. Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided by RETURN trained staff, who are delegated and qualified to do so.

Due to the type of intervention and type of follow up required, patients without capacity to consent for themselves will not be considered as potentially eligible for the trial or approached for consent.

The RETURN Participant Information Sheet and Consent form (PISC), describing in detail the trial intervention, procedures and risks will be approved by an independent REC and the patient will be asked to read and review the document. The PISC and the discussion with the patient will emphasise that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. The PISC will also include a contact point where further information about the trial may be obtained.

Upon reviewing the PISC, the patient will be given opportunity to ask any questions that may arise, have the opportunity to discuss the trial with their relatives / friends and time to consider the information prior to agreeing to participate. However, as RETURN is looking at patients who attend for a one-off urgent dental care visit, once the patient has had their first urgent care treatment (for which they attended the RETURN site) there will be no further opportunity to consent to the trial.

If a patient decides that they would not like to participate, or they would not like to make the decision at their urgent dental treatment, then no further discussions / follow up for consent will be completed. The right of the patient to refuse consent to participate in the trial without giving reasons will be respected.

Only after a full explanation has been given about the intervention, and any queries answered satisfactorily, should the patient consent to the trial. To do this the patient must personally sign and date the informed consent form. Once the patient has completed the consent form, the person who sought consent must then personally sign and date the form. The fully completed original informed consent document will be filed in the RETURN site file, one copy will be given to the participant for their records and a further copy should be provided to the PHPS for filing. Patient consent forms will always be sent to the PHPS separately to any participant trial data.

Since it will not always be possible to record details in electronic clinical notes i.e. for those participants recruited at dental practices, a separate site-specific log (RETURN Participant Log), will be completed, by RETURN trained staff, for each patient recruited into the trial. This will capture the following information:

- Participant name
- Confirmation that consent process was carried out
- Confirmation of participant eligibility
- Randomisation number
- Confirmation of participant recruitment into the trial
- Confirmation of which group (intervention or control) the participant was allocated to
- Date

The participant may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this trial or withdraw at any time.

## Eligibility Assessment and Confirmation

A delegated member of the RETURN trained staff must complete the assessment and confirm eligibility, prior to completing the baseline assessments and randomising the patient. Confirmation of eligibility must be recorded on the case report form (CRF) and on the RETURN Participant Log maintained by the RETURN trained staff.

## Pre-Randomisation Information Provided by Participant

The following pre-randomisation information should be collected as per the Schedule of Assessments (Section 10.8). These include the following:

- Demographic information:
    - Sex
        - Male / Female
    - Age
    - Ethnicity

- Socio-economic information:
    - Education Level
    - Employment status:
        - In paid employment Yes/No
    - Benefit status

- OHIP-14 – 14-item oral health-related quality of life questionnaire

- EQ-5D-5L – 5-item generic quality of life questionnaire

- Modified Dental Anxiety Scale (MDAS) – 5-part dental anxiety questionnaire

- Protection Motivation Theory questionnaire*:
    - Susceptibility of developing urgent dental problems
    - Response efficacy for attending for planned care – that this would reduce the chance of developing an urgent dental problem
    - Severity – not attending for planned dental care means they would at risk of tooth loss, bad breath, or getting an abscess
    - Self-efficacy of attending for planned dental care
    - Intention to attend for a planned care appointment

- Halitosis questions (a PROM measure)

- Bad taste questions (a PROM measure)

- Prescription information – prescription of antibiotics and/or analgesics for dental problems by a dental or medical practitioner within the last 6 months.

***All participants must complete the Protection Motivation Theory questionnaire again <u>after</u> viewing the participant 'thank you' video.**

The participant can proceed to randomisation once the all pre-randomisation information above has been completed.

## Randomisation / Registration

### 10.1.1 **Randomisation Process**

Participants will be randomised to receive either the RETURN Intervention or standard care in a ratio of 1:1 once:

a. Fully informed written consent has been obtained;
b. Eligibility criteria have been fulfilled;
c. Pre-randomisation information has been provided by the participant

### 10.1.2 **Electronic Randomisation**

Participants will be randomised via a secure (24-hour) web-based randomisation programme managed centrally by the LCTC.

A personal login username and password provided by the LCTC will be required to access the randomisation system. RETURN trained staff will be issued with their personal login and password upon completion of training in the use of the system and signature on the delegation log. This training will be coordinated by the LCTC.

When the system requirements (consent and eligibility) are confirmed, the participant allocation and a unique trial number (randomisation number) will be displayed on a secure webpage. An automated email confirmation will be sent to the authorised randomiser, PI and TC (TC). It is the responsibility of the PI and delegated RETURN Intervention trained dental team members and/or research nurses, to ensure they are able to provide the RETURN intervention to the participant after randomisation has been completed.

**Randomisation: web access https://ctrc.liv.ac.uk/Randomisation/RETURN**

*If there are any problems with the randomisation systems contact the LCTC on 0151 795 8759, or via email on returntr@liverpool.ac.uk*

(Note that the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and University of Liverpool closure days)

### 10.1.3 **Randomisation System Failure**

#### 10.1.3.1 **Central Randomisation**

In the event of a randomisation system failure, the centre should contact the coordinating team at the LCTC (Monday to Friday between 9:00 to 17:00, excluding bank holidays and University of Liverpool closure days) to try to resolve the problem. If the problem cannot be resolved, the LCTC will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a standalone PC at the LCTC.

#### 10.1.3.2 **Emergency Back-Up Randomisation Envelopes**

Sites will be provided with emergency back-up randomisation envelopes to be used in the event of a web-based system failure, either if it occurs outside LCTC office hours or if the problem cannot be resolved in a reasonable timeframe. In the event that emergency back-up randomisation envelopes are required, the RETURN trained staff member should select the next sequentially numbered, opaque, sealed envelope. This should then be opened and the randomisation form inside removed, this will contain details of the allocation. The RETURN trained staff should then complete the randomisation form and then inform LCTC as soon as possible to report the use of the backup randomisation envelope. The randomisation form should then be inserted into the Investigator site file.

A delegated RETURN trained staff member will check to ensure that the correct number of randomisation envelopes are present, that they are intact and that the sequential numbering system is maintained. Any discrepancies should be immediately reported to the LCTC.

### 10.1.4 **Participant Contact Details**

Following randomisation, the participant will be asked to provide information which will be directly entered onto the contacts database by RETURN trained staff. The questionnaire will request completion of the following details:

- Patient trial ID number
- Title
- Participant Forename
- Participant Surname
- RQ6 Number (for those recruited at the Dental Hospital Only)
- Date of Birth
- Telephone number
- Email address
- Postal address (including postcode)
- Participant password for online RETURN Intervention access (for those participants randomised to receive the RETURN intervention only).

**Note**: This information is required for follow-up contact and to determine Index of Multiple Deprivation (IMD). As this information is identifiable, it will be stored separately to trial data within a secure (password protected) contacts database.

## Intervention Information

A delegated member of the RETURN site staff must complete the following assessments and record them on the CRF for participants who have received the RETURN intervention:

- **Participant's goal and action plan**; recorded as part of the RETURN intervention
    - This will be photographed using the Tablet PC with only the participant ID number recorded as identifiable information. It will be uploaded to the trial database and accessed by the Central RETURN Team to enable personal tailoring of the follow-up text and phone call.
- **Timing of the intervention**; delivered before, or after, urgent care appointment.

## Participant Reimbursement

Participants in both intervention and control groups will be given a total of £50 in shopping vouchers for reimbursement for their time participating in the trial. The baseline voucher will be given to participants at their baseline visit, subsequent vouchers will be provided to the participants' home address and in accordance with the below schedule:

| Timepoint | Voucher Value |
|---|---|
| Baseline Completion | £15 |
| 6 Month Follow-Up Completion | £10 |
| 12 Month Follow-Up Completion | £15 |
| 18 Month Follow-Up Completion | £10 |
| In-depth Follow-Up Interviews* | Additional £15 per interview |
| Qualitative Dental Team (staff) Interviews** | £15 |

** 35 participants in the RETURN Intervention Group and 15 participants in the Control Group will be invited to take part in in-depth follow-up interviews at around 6, 12, and 18-months follow-up.*

** These are payments for the second component of the qualitative work discussed in 10.8.1.5. There will be at least 30 from 5 separate sites.

## Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

| | | | | | Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|
| Procedures | | Screening / Baseline | RETURN Intervention Group | Control Group | **Within 2 weeks of intervention** | 6 months (+/- 4 weeks) | 12 months (+/- 4 weeks) | 18 months (+/- 4 weeks) |
| Assessment of Eligibility Criteria | | X | | | | | | |
| Signed consent form | | X | | | | | | |
| Urgent dental treatment | | (X) | (X) | (X) | | | | |
| Collection of Contact Details, including Home Postcode (to determine IMD as a mediator) | | X | | | | | | |
| Verification of NHS BSA Matching Descriptors | | | | | | X[6] | X[6] | X[6] |
| Collection of RQ6 number[2] | | X | | | | | | |
| ***Self-Reported Assessments*** | Socio-economic status (Education level, employment and benefit status) | X | | | | X[3] | X[3] | X[3] |
| | Age | X | | | | | | |
| | Gender (including 'prefer not to say') | X | | | | | | |
| | Ethnicity | X | | | | | | |
| | OHIP-14 | X | | | | X | X | X |
| | Halitosis and Bad Taste | X | | | | X | X | X |
| | EQ-5D-5L questionnaire | X | | | | X | X | X |
| | Protection motivation theory questionnaire | X | X[4] | X[4] | | X | X | |
| | Modified dental anxiety scale (MDAS) | X | | | | X | X | X |
| | Use of Routine Dental Practices and Type (NHS or Private) | X | | | | X | X | X |
| | Use of Student Teaching Pathway (Dental Hospitals) | X | | | | X | X | X |
| | Use of Dental Care Practices, including access centres) | X | | | | X | X | X |
| | Attendance at a dental service at baseline, and any subsequent urgent, or planned, dental care at follow-up | X | | | | X | X | X |
| | Use of General Medical Practice for Urgent Dental Care | X | | | | X | X | X |
| | Use of A&E for Urgent Dental Care | X | | | | X | X | X |
| | Hospital In-patient Care for Dental Problems | X | | | | X | X | X |
| | Hospital Out-patient Care, including Dental Hospitals | X | | | | X | X | X |
| | Prescription of antibiotics and/or analgesics within the last 6 months | X[5] | | | | X[5] | X[5] | X[5] |
| | Health Economics Participant Questionnaire (including cost of dental treatment, expenses due to dental care, days off work, travel expenses, non-prescription medications [CSRI]) | | | | | X | X | X |
| Participant randomised and allocation provided | | X[1] | | | | | | |
| Administration of RETURN Intervention | | | X | | | | | |
| Record Intervention Delivery Timing (before, or after, urgent care treatment) | | | X | | | | | |

| | | | | | Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|
| Procedures | | Screening / Baseline | RETURN Intervention Group | Control Group | **Within 2 weeks of intervention** | 6 months (+/- 4 weeks) | 12 months (+/- 4 weeks) | 18 months (+/- 4 weeks) |
| Participant's Goals and Action Plan | | | X | | | | | |
| Participant 'thank you' video | | | X | X | | | | |
| Participant Voucher Reimbursement | | | X | X | | X | X | X |
| Text Message Reminder | | | | | X[7] | X[8] | X[8] | X[8] |
| ***Dental team*** | Date of urgent dental care visit, participant sex and date of birth. | X[5] | | | | | | |

*(X) completed when appropriate*

*[1]Allocation must only be provided after all self-report baseline assessments have been completed.*

*[2] Participants recruited in Dental Hospitals only.*

*[3] Employment status only*

*[4] RETURN Intervention and Control Groups to complete second protection motivation theory questionnaire after being shown the thank you video.*

*[5] Self-reported prescription of antibiotics by dentists verified against participants' records with permission, using BSA data for participants recruited at Dental Practices, or record audits for participants recruited at a Dental Hospital.*

*[6] Participant name, date of birth and postcode. If participant postcode has changed from baseline, then the month that the participant changed their address should also be collected.*

*[7] Text message will contain reminder of goals and link to website*

*[8] Text message will be a reminder of incoming call for study*

## Follow-Up Schedule – 6 months (26 weeks), 12 months (52 weeks) and 18 months (78 weeks) post-randomisation (+/- 4 weeks)

Participant follow-up will occur at 6 months (26 weeks), 12 months (52 weeks) and 18 months (78 weeks) by a trained researcher from the Central Follow-Up Team based at the Department of Public Health Policy & Systems at the University of Liverpool, who will enter the data directly into the trial database (if follow-up is completed by telephone or post) using a username and password. If follow-up is completed by email, the data will be directly entered into the database by the participant. At each follow-up, the below self-reported assessments will be captured:

- Socio-economic status
  - Employment status only; currently employed Yes/No
- OHIP-14
- Halitosis questions
- Bad taste questions
- Attendance at a dental service at baseline and any subsequent urgent, or planned, dental care (whether NHS/Private dental practices, or Hospital Student Dental Clinic) within the last 6 months
- Type and volume of dental treatments received at any urgent, or planned, care appointments (whether at NHS/Private dental practices, or Hospital Student Dental Clinics) within the last 6 months
- EQ-5D-5L questionnaire
- Health economics participant questionnaire (CSRI)
  - Number of healthcare contacts within the last 6 months for teeth / mouth problems – by person or telephone/e mail

        - GP
        - A&E (either hospital or walk in centres)
        - Hospital In-Patient
        - Hospital Out-Patient including the Dental Hospital
        - Dental practice,
        - Dental access centre or an urgent dental care practice in hours
        - Out of hours urgent dental care service (evening and weekends)
        - Other
    - Medications taken within the last 6 months for teeth / mouth problems
    - Non-prescription medication taken in the last 6 months for teeth / mouth problems
    - Travel expenses associated with teeth / mouth problems in the last 6 months
    - If employed number of days off work in the last 6 months due to teeth / mouth problems
    - If employed, estimated earnings lost in the last 6 months due to teeth / mouth problems
    - Payments made by the participant for dental treatment within the last 6 months
    - Any other expenses in the last 6 months due to teeth / mouth problems
- Protection Motivation Theory questionnaire *(6- and 12-months follow-up only)*
    - Susceptibility of developing urgent dental problems
    - Response efficacy for attending for planned care – that this would reduce the chance of developing an urgent dental problem
    - Severity – not attending for planned dental care means they would be at risk of tooth loss, bad breath or getting an abscess
    - Self-efficacy of attending for planned dental care
    - Intention to attend for a planned care appointment
- Modified Dental Anxiety Scale (MDAS) – 5-item dental anxiety questionnaire

The researcher will confirm IMD on the home postcode and make any required amendments in the contacts database. At the 6, 12 and 18-month follow-up contact, the participant should verify the NHS BSA key matching descriptors; name, date of birth and postcode. If the participant changed their postcode since baseline, they will be asked to provide the month in which their postcode changed.

It is expected the follow-up telephone call, or other method of follow-up (email, questionnaire) will take approximately 15-20 minutes to complete.

All intervention participants will be sent text message reminders. One will be received within 2 weeks of intervention delivery reminding them of their action plan and goals. The others will be the week before their 6,12 and 18 month follow up and will remind them of the upcoming contact.

#### 10.1.4.1 **Method of Contact**

Where possible, contact will be via participant phone number i.e. telephone will be used as the first method of contact. In cases where a phone number was not supplied, contact will be made via email (if provided) or post. Where participants only give one contact type, this will be used. Tracking of contact to the participants will be completed by the central follow up team. Questionnaires will be posted to the central follow-up team who will complete the data entry required. Postal questionnaires will be used as a last resort, where there is no response to telephone calls and where there is either no e-mail address given, or no response to e-mails.

**Telephone Follow-Up:**

A telephone follow-up will be made to all participants where a telephone number is provided (both control and intervention group participants). Before the telephone call is made a text will be sent via the RETURN trial mobile phone to the participant to let them know to expect an incoming call from the research team (since the number may not be recognised as one of their contacts). This will minimise the risk of participants not answering the research call.

The telephone call will be conducted as a semi-structured interview to enable the researcher to complete the required questionnaires. All telephone calls will be audio-taped with the participants' permission (collected on the PISC at recruitment) to facilitate accuracy-checking of the recorded responses. Participants will be

reminded about permission to audiotape at the beginning of the call. If participants decline to have their telephone call recorded, the telephone call will continue, and notes will be taken by the researcher. Transcribing of the call data into data fields and free text will be validated by duplicate transcribing of a random sample of 10% of the calls, where two members of the RETURN research team will independently accuracy-check the follow up data by listening to the audio-recordings, and checking against the responses recorded. Any discrepancies in transcribing between audiotape and the CRF will be identified, corrected and reported. If an error rate of >20% is detected, all audio-recordings and data will be accuracy-checked. These recordings will be made and stored on a password-protected device.

Up to 5 telephone call attempts will be made. If no contact is made by telephone, or no telephone number is available, attempts will then be made to contact them first by e-mail and then by post. Because the window for follow up is 4 weeks, emails/ postal contact may be started before all 5 attempts at telephone contact have been exhausted.

**Email Follow-Up:**

Where the participant provided an email address, an email will be sent with a link to the questionnaire. A cover email will accompany the link providing any necessary participant information including a reminder of what the questionnaire is for. Up to 3 attempts at contacting by email will be made.

**Postal Follow-Up:**

For those not responding to telephone contact or e-mails/no e-mail address is available, and for those participants who provide a postal address, up to 3 postal questionnaires will be sent before the participant is recorded as lost to follow up. A cover letter will accompany the questionnaires providing any necessary participant information including a reminder of what the questionnaire is for. Postal questionnaires will contain a pre-paid envelope to facilitate their return to the Central RETURN Team. The postal questionnaire will be issued using the participant trial ID number and will not contain any other identifiable information such as name and address.

Further information about the qualitative elements assessed via this follow up are detailed in Section 10.8.2.4.

**Distress Policy**

A distress policy will be implemented for all participants of the trial.

<u>Within the Dental Practice</u>
Where distress is communicated by a participant at the baseline visit, (either if the participant responds to EQ-5D-5L as “I am extremely anxious or depressed” or otherwise communicated during the research visit) the nurse will recommend the participant contact their GP/ call NHS 111/ or contact the Samaritans on 116 123 to seek help.

If a safeguarding issue were to arise that warranted a confidentiality breach and a referral to other services such as the Police/GP/Social Services during the course of the research activities, the dental teams will follow usual safeguarding processes as appropriate within their dental setting.

<u>At follow-up</u>
Where distress is communicated by the participant at the telephone follow-up (either if the participant responds to EQ-5D-5L as “I am extremely anxious or depressed” or otherwise communicated), the researcher will recommend that the participant contact their GP / call NHS 111 or contact the Samaritans on 116 123 to seek help.

If a safeguarding issue were to arise during the telephone follow-up that warranted a confidentiality breach and a referral to other services such as the Police/GP/Social Services, then the researcher will immediately contact the CI who will make the necessary referral. Participants may be asked to provide their GP details in this instance.

10.1.4.2 **Efficacy Assessments**

**BSA Data**

The BSA database should contain information regarding participant dental visits, including but not limited to:

- Date of dental visit
- Treatment provided
- Antibiotic prescription data

**Baseline visit:**

BSA Data will be requested using participant name, date of birth, gender and post-code following provision of explicit consent for this. The request will be for the following data:

- Date of visit for urgent care
- Contract number for the dental service

**BSA data on subsequent care:**

- Date of visit
- Contract number for the service (whether appointment is for urgent or planned dental care: Band 1 (urgent) / Band 1 / Band 2 / Band 3) (secondary objective 1 and 2)
- Start date and finish date of treatment plan
- Treatment items provided
- Whether antibiotics were prescribed by either a dental practitioner, or general medical practitioner

10.1.4.3 **Dental Hospital Data**

Dental Hospitals do not routinely provide information to BSA for database inclusion. Data will be requested using participant name, date of birth and if available a unique hospital identifier (RQ6 number) following provision of explicit consent for this.

**Baseline visit:**

For patients recruited from Dental Hospital the following data will be collected on the CRF.

- Visit for Urgent Dental Care (Yes/No)
- Date of Visit

**Subsequent visits:**

Using the RQ6 code for participants recruited in the Dental Hospital, or name, gender and date of birth for other participants recruited in dental practices, data on subsequent attendances at the Dental Hospital for urgent or routine care will be gathered using the clinical record system.

**Visit for further Urgent Dental Care:**

- Date of Visit
- Attendance for Routine Care (Yes/No)
- Failed appointments for routine care
- Date attendances routine care
- Whether for student or staff care
- Treatment items provided
- Prescription data for antibiotics or analgesics

10.1.4.4 **CSRI**

The RETURN CSRI form is adapted from the CSRI (Beecham 1999). It is informed by the literature and developed in conjunction with the RETURN Programme Advisory Committee and Patient Reference Group (which is advisory to the Programme Management Group). It includes questions regarding out-of-pocket expenses (e.g. travel, extra child-care occurring as a result of dental/oral health problems, prescriptions and over the counter medicines) and absence from paid employment.

10.1.4.5 **Qualitative Trial Components**

There is an embedded qualitative component to the trial, In-depth interviews are planned with at least 50 recruited patients (35 in the intervention and 15 in the control arm), around the time of the three follow up points (6, 12, 18 months post-intervention). These interviews will explore issues in depth, gathering information on the impact and meaning of the intervention in the wider context of people's lives. This component of the programme will give us insight into changes in dental visiting patterns longitudinally, and factors in people's lives linked to these. This component will also give us insight into the service-related factors which contribute to inequalities in oral health. While service-related factors are beyond the scope of the programme, following the experience of users who take up dental care, enables us to describe any subtle bias experienced when taking up routine dental care, against users from low SES backgrounds.

The aim of the qualitative in-depth interviews is to assess: (1) whether the intervention has made a difference, whether it was found to be useful and meaningful, and to explore what any active ingredients of the intervention have been, (2) participants' life-course dental visiting patterns (at the first in-depth interview at 6 months) and relevant factors in their lives which led to changes in dental visiting, and (3) participants' experiences of taking up routine dental care after previously using urgent dental care, or for those participants who have not taken up routine care, factors in their lives that hinder dental visiting and potential changes in this at the different follow-up points, (4) whether patients who take up planned care in student clinics have different characteristics and issues compared with patients who take up routine NHS dental practice. These interviews will be audio-recorded and transcribed verbatim. Then, the interviews will be analysed thematically. Patients will be given the information about a possibility of being invited to participate in the in-depth interviews at the time of enrolment, although patients will be given the option to opt out of this part of the study. Theoretical sampling will be used to determine which patients are invited to take part in the in-depth interviews: we will aim for a range of age and gender, and experience of barriers to dental care as identified in the goals and actions plans completed by participants, as well as responses to the 6 month follow-up call for the main trial.

Two qualitative components form the trial. The first qualitative component takes place at 6, 12 and 18 -month follow-up, and involves a semi-structured interview, either face-to-face in the participant's home or another location suitable to them, or by telephone.

The second component uses face-to-face or telephone semi-structured interviews with dental team members, taking place during or after the recruitment phase. The face to face or telephone interviews will take place in order to gather the insights from the dental team in the practical issues of delivering the intervention in this setting, and how they feel the intervention is received. At least 30 dental team members will be interviewed in at least 5 different sites. Participants will be reimbursed £15 in vouchers for their time.

A member of the Central Research Team will also observe delivery of the intervention in order to gather data on intervention fidelity. At least 20 intervention deliveries will be observed. Observations will be recorded in field notes.

Selected audio extracts from the qualitative section of the follow up calls will be used from some of the participants for the purpose of dissemination of results. At the time of consent permission was obtained to audio record the follow up phone calls, and their ongoing consent procedure in place. Additional verbal consent will be sought for selected participants to use the audio extract. This verbal consent will be recorded on a log by the researcher and the consent itself will be audio recorded and stored securely.

### 10.1.5 **Safety Assessments**

Active monitoring of safety events experienced by trial participants will take place from randomisation, until the end of participant follow-up at 18 months (+/- 4 weeks). Reportable safety events will include:

- An exacerbation of a dental anxiety that meets the serious criteria
- An adverse event related to the trial procedures

### 10.1.6 **Quality of Life Assessments**

EQ-5D-5L (5 item generic quality of life) and OHIP-14 (14 item oral health-related quality of life) self-reported questionnaires will be completed by participants at Baseline, 6-, 12- and 18-month follow-up time points.

### 10.1.7 **Health Economic Assessments**

The CSRI (adapted for RETURN) will be completed by participants at the 6-, 12- and 18-month follow-up time points.

## Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

### 10.1.8 **Withdrawal from Trial Intervention**

Participants may discontinue the intervention for reasons including, but not limited to:

- Participant-led i.e. request by the participant
- Insufficient time to complete the intervention
- Any change in the participants condition that justifies discontinuation of the intervention in the opinion of the person providing the intervention, the PI, or the participant.

If a participant wishes to withdraw from the trial intervention (i.e. does not want to receive the intervention), sites should explain the importance of remaining in trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes.

Discontinuation from trial intervention does not mean discontinuation of the trial altogether, and the remaining trial procedures, follow up assessment / visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn, see Section 10.9.3 below).

### 10.1.9 **Participant Discontinuation from Follow Up**

Participants are free to withdraw from follow up at any time without providing a reason. If participants express a wish to discontinue their participation in the trial follow up, the research team at site or RETURN trained researcher should ascertain if this is for all elements of trial follow-up, or if for example data from routine assessments can still be collected (NHS BSA). If the participant wishes to completely withdraw consent, see 10.1.10. If the participant is happy for us to continue to collect NHS BSA data they are classed as a 'participant discontinuation'.

Participants who no longer wish to continue with follow-up will have data collected up to the point of discontinuation included in the analyses. The participant will not contribute any further data to the trial and the PHPS (TM) should be informed by the researcher as soon as they become aware.

In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the PHPS via processes detailed in Section 11.11, even if a participant has withdrawn from follow-up.

### 10.1.10 Complete Withdrawal from Trial

Participants are free to withdraw consent at any time without providing a reason, though a reason should be recorded if one is given. Participants who wish to withdraw consent for the trial will have pseudo-anonymised data collected up to the point of that withdrawal of consent included in the analyses. The participant will not contribute further data to the trial (apart from that mentioned in Section 10.9.1 above) and the TM should be informed as soon as possible and the Withdrawal eCRF should be completed within 7 days.

Any SAEs will be notifiable to the CI and LCTC via processes detailed in Section 11.11 even if a participant has withdrawn from follow up.

### 10.1.11 Loss to Follow-up

A participant will be considered lost to follow up if s/he is not contactable by the site research team. The following information will be collected where possible/available, on the contact database at the baseline visit to allow telephone follow-ups to occur:

- Contact telephone number and/or email address and/or postal address.

  **N.B.** Postcode will be collected for all participants, where possible, to be able to derive IMD.

- Preferred dates and times for follow-up telephone calls.

Participants will be contacted a maximum of five times by telephone to collect follow up information and then by email (if available) and by post. If no response is received by any available means, then these participants will be considered as lost to follow-up. However, matching with BSA data will continue unless the participant confirms that they would like to withdraw consent (see Section 10.9.3).

## End of Trial

The end of the trial is defined to be the date on which data for all participants is locked and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Programme Management Group (PMG), on the recommendation of the Programme Steering Committee (PSC).

Site and closure activities will be centrally coordinated and conducted by PHPS regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and HRA
- Trial-related materials reconciled and returned/disposed of as appropriate
- All site data entered onto the trial database, discrepancies raised, and satisfactory responses received
- Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

# 11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

## Terms and Definitions

| | |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. |
| **Related Adverse Event (Related AE)** | An AE resulting from administration of any of the research procedures |
| **Serious Adverse Event (SAE)** | An AE is termed serious if it:<br>• results in death;<br>• is life-threatening:<br>*N.B. "life-threatening" means the subject was at immediate risk of death at the time of the event; it does not describe an event which may hypothetically have resulted in death had it been more severe;*<br>• requires hospitalisation, or prolongs existing hospitalisation:<br>*N.B. Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, are not considered "serious";*<br>• results in persistent or significant disability or incapacity:<br>*N.B. Substantial disruption of one's ability to conduct normal life functions;*<br>• consists of a congenital anomaly or birth defect:<br>• an otherwise medically significant event which jeopardises the subject or requires intervention to prevent any of the above. |
| **Related Serious Adverse Event (Related SAE)** | An AE assessed as **related** and **serious** |
| **Related Unexpected Adverse Event (RUAE)** | An AE which is assessed as **related** and **unexpected** |
| **Related Unexpected Serious Adverse Event (RUSAE)** | An AE which is assessed as **related** and **unexpected** and **serious** |

## Assessment of Seriousness

The assessment of seriousness of safety events should be performed bthe CI at follow up, and an appropriately delegated, qualified RETURN trained staff member.

A [#]safety event (whether or not assessed as related to the trial) is assessed as serious if it:

- Results in death;
- Is life-threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of trial participants, or their partners, regardless of time of diagnosis), or
- Is otherwise considered medically significant by the investigator.

[#]*safety event / reaction applies apply to either AEs, or ARs, or Related AEs, or Adverse Device Effects*

## Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by a suitably qualified and delegated dentist, responsible for the care of the participant, using the definitions in the table below:

*Table 1: Severity Grading*

| Severity | Description |
|---|---|
| **Mild** | Does not interfere with routine activities. |
| **Moderate** | Interferes with routine activities. |
| **Severe** | Impossible to perform routine activities. |
| **Life-Threatening** | Causes immediate threat to life. |
| **Death** | Event results in death. |

**N.B.** A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 11.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

## Assessment of "Causality" - Relationship to Trial Intervention

The assignment of the causality should be made by a suitably qualified and delegated dentist, responsible for the care of the participant, using the definitions in the table below:

*Table 2: Definitions of Causality*

| Relationship | Description |
|---|---|
| **Unrelated** | There is no evidence of any causal relationship.<br>N.B. An alternative cause for the AE should be given |
| **Unlikely** | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention).<br>There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment). |
| **Possibly** | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention).<br>However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments). |
| **Probably** | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| **Almost certainly** | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |

In the case of discrepant views on causality between the dentist and others, the opinion of the treating dentist will never be downgraded, and the REC will be informed of both points of view. Only adverse events that a possibly, probably or almost certainly related will be reported.

## Assessment of "Expectedness"

The CI for the RETURN Main Trial is responsible for determining whether a safety event is expected or unexpected, however a CI will not assess their own patients, these patients will be assessed by the Dentist at site. An AE whose causal relationship to the intervention is assessed by the dentist as "possibly", "probably", or "almost certainly" is considered to be a related AE and will be classified by the CI or delegated other as unexpected. If also graded as serious, the event should be reported as an RUSAE.

## Time Period for Active Monitoring of Safety Events

All related AEs should be followed until satisfactory resolution or until the dentist responsible for the care of the participant deems the event to be chronic or the patient to be stable.

**IMPORTANT:** Any safety events occurring after the end of the below described "active monitoring" period which meet the definition of serious (see Section 11.2) and are recorded for this trial (see Section 11.7) must continue to be reported by sites or central follow-up team researchers to PHPS in accordance with the timeframes and procedures described in Section 11.12. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from randomisation, until the end of participant follow-up at 18 months (+/- 4 weeks).

## Notes on Safety Event Recording Inclusions and Exclusions

Due to the type of intervention, related adverse events are not expected. Dental anxiety is measured separately using the MDAS and therefore will not be reported separately as an adverse event, unless deemed serious.

AEs reportable on RETURN, if assessed as related, include:

- An exacerbation of a dental anxiety that meets the serious criteria
- An adverse event related to the trial procedures

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

## Notification of Deaths

If the site become aware of the death of a participant (whether related to the trial or not) this should be notified to PHPS using the Death CRF **within 24 hours** of becoming aware. RETURN trained staff must also confirm the death of the patient on the Withdrawal CRF, and on the RETURN contact database, preventing any further contact with the bereaved family.

## Reporting Procedures

All related AEs should be reported. Depending on the nature of the event the reporting procedures below should be followed.. A flowchart is given in Section 11.12 to aid in determining reporting requirements.

All reportable adverse events should be followed until satisfactory resolution or until the Investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

## Related Adverse Events

All such events should be recorded on a related AE Form, which should be transmitted to the LCTC **within 7 days** of the awareness of the issue.

## Serious Adverse Events / Related Unexpected Serious Adverse Events

Related SAEs and RUSAEs should be reported **within 24 hours** of the local site, or Central Research Team, becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The reporting dentist should sign the causality of the event. Additional information should be sent **within 5 days** if the event has not resolved at the time of reporting. As a minimum, the SAE form should contain the following information:

- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- One related SAE
- One suspect intervention (the RETURN intervention)
- A causality assessment

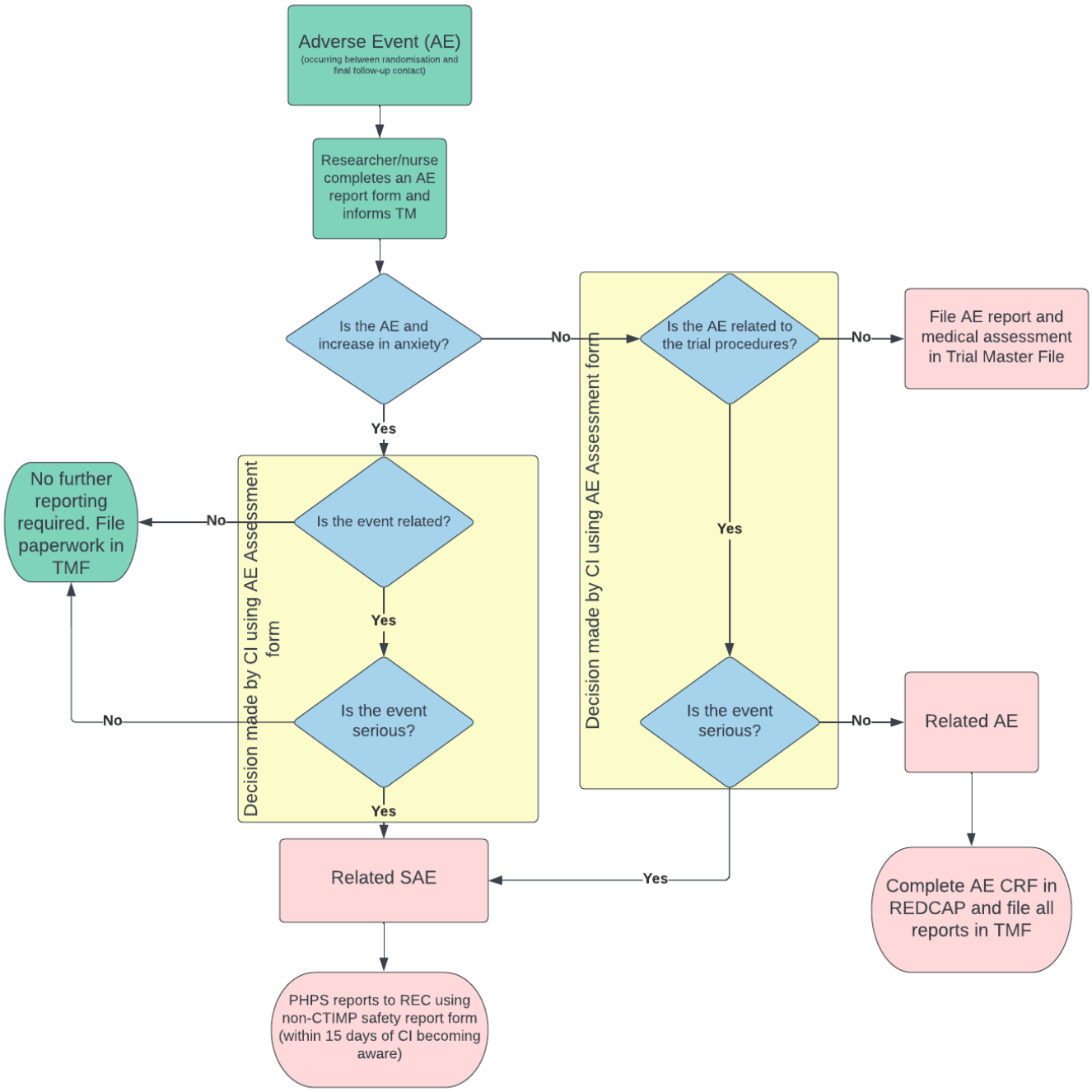
The PHPS (RETURN TM) will notify the REC of all RUSAEs occurring during the trial **within 15 days**. All dentists will be informed of all RUSAEs occurring throughout the trial. Local dentists should report any RUSAEs as required locally.

When reporting RUSAEs, the reporting dentist should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

SAEs must be subsequently followed up in line with the processes below:

- Follow up must continue until clinical recovery is complete or until the event has stabilised (see Section 11.13). **N.B.** Follow-up may continue after completion of protocol treatment if necessary.
- Follow-up information is noted on a new SAE form
- Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.

## Flowchart for Site/Central Follow-up Team Reporting Requirements of Adverse Events




## Investigator (Dentist) and Central Follow-up Team Reporting Responsibilities

At each participating site there will be a designated investigator named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial-related medical decisions.

Follow up appointments are conducted by the central research team and any related adverse events will be flagged to the CI or other delegated dentist for assessment.

If any related adverse events are notified to or observed by the research teams at any participating sites or members of the central research team, it must be reported by the investigator using the appropriate form.

AEs that do not meet the criteria of 'serious' must be recorded on an AE form to be reported to the LCTC within **7 days**.

All related SAEs must be reported **immediately** to the LCTC on an SAE form.

The SAE form should be completed by a designated investigator who should record the assessment that the SAE is a response to the intervention. In the absence of the designated investigator, the form should be completed and signed by an alternative RETURN trained staff member and submitted to the LCTC. As soon as possible thereafter, the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed reports as appropriate.

SAE forms should be sent by a secure method, such as an encrypted email (within 24 hours or next working day) to the TM.

**Email: lctcsafe@liverpool.ac.uk**

When submitting an SAE to the LCTC the reporter should also telephone the appropriate Data Manager on telephone number **0151 795 8766** to advise that an SAE report has been submitted.

Sites must follow any standard local governance procedures regarding local reporting processes e.g., notifying the R&D department (for the Dental Hospital) or Practice Manager (for dental practices) of the event.

**N.B.** The patient must be identified by trial number, age, and initials only. The patient's name should not be used on any correspondence.

## PHPS Responsibilities

The PHPS department is undertaking trial management duties delegated by the trial Sponsor, the University of Liverpool. PHPS are responsible for the reporting of RUSAEs and other related SAEs to REC as follows:

- RUSAEs within 15 days of the PHPS first becoming aware of the event.
- A list of all related SAEs (expected and unexpected) must be reported annually.

The TM will liaise with the CI (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality.

Investigator reports of suspected related SAEs will be reviewed immediately and those that are RUSAEs identified and reported to REC.

The causality assessment given by the local Investigator at the participating site cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The dentists at all sites participating in the trial will be notified of any RUSAEs.

### 11.1.1 **Safety Reports**

Safety reports will be generated during the course of the trial to allow for monitoring of SAE and related AE reporting rates by site. The TM will send Annual Progress Reports (APRs) containing a list of all related SAEs to REC. Any concerns raised by the PSC, or inconsistencies noted at a given site, may prompt additional training at sites, with the potential for the PHPS to carry out site visits if there is suspicion of unreported related AEs in patient notes. Additional training will also be provided if unacceptable delay in safety reporting timelines is noted. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

### 11.1.2 **Urgent Safety Measures (USMs)**

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC.

PHPS will notify the REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC. If the trial is temporarily halted it may not recommence until authorised to do so by the REC. If the trial is permanently terminated before the date specified for its conclusion (in the original applications to REC, the Sponsor should notify the REC within 15 days of the date of termination by submitting the formal End of Trial Notification.

## Contact Details and Out-of-hours Medical Cover

Due to the type of intervention, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for RETURN Main Trial participants. All participants will be provided with a copy of the information sheet which includes information about their participation and contact details for the local RETURN trained staff who may be contacted if necessary. During office hours, the CI or delegate are able to provide advice in relation to participation using the contact details listed at the beginning of this document.

# 12 STATISTICAL CONSIDERATIONS

## Introduction

A full detailed Statistical Analysis Plan (SAP) and Health Economics Analysis Plan (HEAP) will be developed prior to the analysis of the main trial. The main features of these planned statistical analyses are included here in the protocol.

## Sample Size

### 12.1.1 Sample Size Calculation

Based on previous data we estimate that 30% of urgent dental care users will return for planned dental care within 12 months. The calculation is based on a minimum clinically important difference of 10 percentage points (i.e. an improvement to 40% of patients attending a dentist) in the first of the joint primary outcomes. We estimate there is a possibility of some contamination between patients within practices. Rather than use a cluster randomised design, we have reduced the difference we want to detect to 9 percentage points to allow for potential contamination. Based on this, a sample size of 559 per group would give 80% power at $\alpha$=0.025 (to allow for joint primary outcomes) to detect this improvement in the intervention group. Allowing for 5% loss to follow-up gives a total target sample size of 590 per group

For the second primary outcome, OHIP-14, we estimate a standard deviation of 11 points at one-year follow-up. We also assume a higher rate of loss to follow-up of 20% for this outcome, as it will require successful telephone follow-up. Based on this, our total sample size of 1180 will give 80% power to detect a minimum clinically important difference of 2.25 points, with $\alpha$=0.025.

## Internal Pilot

**Internal pilot**

An internal pilot is be run within the RETURN main trial focused on the following outcomes:

1. Practice recruitment rates
2. Participant recruitment rates
3. Delivery of training
4. Fidelity of intervention delivery

The internal pilot will run for the first 2 of the 12-month main trial recruitment period and the stop/ go criteria will be assessed by the project steering committee. The following table outlines the required stop/ go criteria for assessment:

| Objective | Outcome Measure | Stop/Go criteria | Improvement Strategy |
|---|---|---|---|
| To identify if practice recruitment and site opening rates are achievable (including the opening of the dental hospital as a site) | Number of sites opened, per month (including the dental hospital) | Number of sites opened is 6 or above after 2 months (including the dental hospital) | Proceed to main phase of trial |
| | | Number of sites opened is between 4 and 5 after 2 months (including the dental hospital) | Explore methods for enhancing practice recruitment and additional support opening sites |

| | | | |
|---|---|---|---|
| | | Number of sites opened is below 4 after 2 months | Consider delaying trial until dental services have more capacity |
| To identify if recruitment rates are achievable across sites and site types | Number of patients recruited across sites, per month | Total recruitment is at least 33 after 2 months (≥100% of expected recruitment) | Proceed to main phase of trial |
| | | Total recruitment is between 26 – 32 after 2 months (80%-99% of expected recruitment) | Explore methods for enhancing recruitment within the sites |
| | | Total recruitment is below 26 after 2 months (<80% of expected recruitment) | Increase number of sites projected to deliver the trial |
| To determine whether the multi-faceted approach to training is successful | Proportion of staff members at each site that achieve competency sign off from all elements of training (online GCP, intervention training (assessed via role play), one day 'on the job' support) | 100% of minimum staff required who undertake training at each site achieve sign off | Proceed to main phase of trial |
| | | 80% - 99% of minimum staff required who undertake training at each site achieve sign off | Further training is delivered, concentrating on ensuring that all providers are up to the same standard |
| | | < 80% of minimum staff required at each site achieve sign off | Review of training package, making changes to improve training standards |
| To determine fidelity of intervention delivery. | Observations and / or independently rated audio recordings of intervention delivery sessions to determine % allocated patients who at least some of the intervention materials | 100% allocated participants engaged with the intervention | Proceed to main phase of trial |
| | | 80% - 99% allocated participants engaged with intervention | Booster training sessions for dental nurses delivering the intervention |
| | | <80% allocated participants engaged with intervention | Re-training of dental nurses, further in-practice support provided by the research team |

# Method of Randomisation

### 12.1.2 **Allocation Sequence Generation**

Participants will be equally randomised to the intervention or control group in a 1:1 ratio using a secure (24-hour) web-based randomisation programme controlled centrally by LCTC. Randomisation lists will be generated using block randomisation with random variable block length, stratified by site. The lists will be produced by an independent statistician (who is not otherwise involved in the RETURN trial) at LCTC.

### 12.1.3 **Concealment and Implementation of Allocation Sequence**

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed.

# Blinding Considerations

RETURN is an open trial and as such investigators involved in the delivery of the intervention and participants in the trial are not blind to allocations.

# Interim Analyses

No formal interim analysis is planned, but there will be regular monitoring by the PSC, who will meet at least annually, and have the option of unblinding if there are concerns about safety.

# Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Participants will be included in the analysis set based on the intention-to-treat principle.

For the first primary outcome of dental attendance for a planned appointment within 12 months, comparison between groups will use logistic regression, adjusted for the stratification factor site. A second analysis will also adjust for other pre-specified baseline variables, including dental anxiety and socio-economic status.

The second primary outcome, OHIP-14 at 12 months, will be analysed using linear regression, adjusted for site, baseline value of OHIP-14, adjusted for the stratification factor site. A second analysis will also adjust for other pre-specified baseline variables, including dental anxiety and socio-economic status. For both primary outcomes consideration will be given to using mixed regression models to allow for random variation between sites.

Secondary outcomes will be analysed using similar methods to the primary outcomes, using either logistic or linear regression, depending on the variable type.

The secondary objective of exploring whether there is a differential intervention effect over the socio-economic gradient will be explored by adding interaction terms between intervention and socio-economic status into the primary outcome regression models and some of the secondary outcome regression models. This analysis will be exploratory, as the trial is not powered to detect these interaction effects.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

Safety data will be reported descriptively.

## Health Economics Analysis Plan

The cost-effectiveness analysis will be undertaken at 12 and 18 months. The primary outcome of the cost effectiveness analysis will be cost per quality-adjusted life years (QALYs). Utility values will be obtained from participants' responses to the EQ-5D-5L questionnaire completed at baseline, and, 6, 12, 18 months. The derived utilities will be used to generate QALYs (Drummond et al, 2015).

Resource use (dental surgery) will be obtained from the Business Health Services Authority BSA. In addition, a participant questionnaire will be administered at baseline, 6, 12, 18 months. The questionnaire includes healthcare used due to problems with teeth, mouth or dentures, include out-of-pocket expenses (e.g. travel, prescriptions costs of antibiotics and analgesics and over the counter medicines) and absence from paid employment.

Productivity costs (time away from work) will use human capital-based estimates (Drummond et al, 2015). Medication cost will be obtained from the British National Formulary BNF and the Drug Tariff. The currency used will be the pound sterling (£).

The within trial analyses aim to assess the incremental cost per QALY gained and will present an incremental cost effectiveness ratio (ICER). The nonparametric bootstrapping approach will be used to determine the level of sampling uncertainty around the ICER. Cost Effectiveness Acceptability Curves (CEAC) will be presented and net monetary benefit (NMB) will be calculated. Sensitivity analyses will include estimation of the cost effectiveness using the trial co-primary outcomes (Oral Health Impact Profile (OHIP-14) and attendance at a dental practice for a planned care appointment within 12 months).

# 13 DATA MANAGEMENT AND TRIAL MONITORING

For the RETURN Main Trial the responsibilities for Data Management and Monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

## Source Documents

A RETURN source document list will be produced for each site confirming the location of source data. Date(s) of conducting informed consent process including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's dental record chronologically. Also available at each site will be paper-based screening logs and paper-based serious adverse event forms. The CRF will be considered as the source if no prior record exists.

## Data Collection Methods

The CRF/eCRF is the primary data collection instrument for the trial (both paper and electronic), so all data requested on the CRF must be recorded and all missing data must be explained. A copy of all CRFs should be retained at site. Any corrections should be made in accordance with GCP.

Questionnaires are a source document and the TC will collect these from the sites rather than transfer these by posting.

Data are to be entered into the RETURN REDCap database by RETURN trained staff members at site. Training will be provided prior to any data entry.

Primary data will be either be collected onto the paper CRF or the trial electronic CRF (eCRF). All data requested on the CRF must be recorded and missing data explained.

For questionnaires, the patients must complete these themselves, or for any follow-up questionnaire completed by email, this would be by computer.

There will be paper-based screening logs, SAE forms and paper-based questionnaires (if 6-, 12- and 18-month follow-up is postal).

## Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial intervention, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see Section 4.

### 13.1.1 **Central Monitoring**

There are a number of monitoring features in place at the LCTC/PHPS to ensure reliability and validity of the trial data, to be detailed in the Trial Monitoring Plan. Details on the data cleaning process will be included in the Data Entry and Cleaning Manual (DECM). Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the LCTC from the trial database and sent either electronically or through the post to a RETURN trained staff member (as listed on the site delegation log). RETURN trained staff members will respond to the queries, providing an explanation/resolution to the discrepancies and return the data query forms to the LCTC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding trial conduct, participant recruitment, outlier data, or other factors as appropriate.

### 13.1.2 **Clinical Site Monitoring**

In order to perform their role effectively, the TC, and researchers involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this trial, a PI grants permission to the Sponsor (or designee), to conduct on-site monitoring and/or auditing of all appropriate trial documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the trial protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

## Risk Assessment

In accordance with the relevant LCTC standard procedures, this trial will undergo a risk assessment, completed in partnership between:

Sponsor representative(s)
Chief Investigator
TM and Supervising TM(s)
Trial Statistician and Supervising Statistician
Information Systems (IS) Team
Data Management Team
LCTC Director

In conducting this risk assessment, the contributors consider potential participant, organisational, and study hazards, the likelihood of their occurrence and resulting impact if they should occur.

The RETURN Trial is determined to be a low risk trial.

## Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection

legislation. Data (including special category) will only be collected, used and stored if necessary, for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

Individual participant medical/dental information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below:

CRFs/eCRFs will be labelled with the patient's initials and a unique trial screening and/or randomisation number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the PHPS by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

**N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.**

Site-specific trial-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The PHPS as part of The University of Liverpool will preserve the confidentiality of participants taking part in the trial. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Leeds University is also considered to be a Joint Data Controller, with respect to the required data for Health Economics analysis.

Breaches of data protection principles or regulations identified by PHPS will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

The RETURN Central Research Team at the Department of Public Health, Policy and Systems will be contacting the patients at follow up and for qualitative interviews. Therefore, they will be required to receive contact details including name, email address and telephone details. The contact information will be added to the RETURN contact database at trial entry by the Central Research Team. The contact database will be maintained securely on password protected computers.

A data sharing agreement will be in place between the University of Liverpool and the NHS BSA to safeguard the confidentiality of personal identifiable data transfer between the two organisations. Data will be transferred using a Secure File Transfer platform.

## Quality Assurance and Control

Quality Assurance (QA) includes all the planned and systematic actions established to ensure the trial is performed, and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. Quality Control (QC) includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled, e.g. state what clinical site monitoring (and audit) is planned, if any. In accordance with the monitoring plan site visits will or will not be conducted and source verification performed if indicated to be require as a result of central monitoring processes.

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.

- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- Independent members of the PSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

## Records Retention

The retention period for the RETURN data and information is 10 years from the official End of Trial date (defined in Section 10.10 above).

The PI at each investigational site should make arrangements to store the essential trial documents (as defined by ICH GCP guidelines), including the Investigator Site File and the applicable participant medical records for the full length of the trial's retention period, and will arrange for confidential destruction at the end of this period as instructed by the Sponsor. It is a possibility that some of the investigational sites may not have the capacity to store essential trial documents for the full length of the trial's retention period. In this instance, archiving may be coordinated centrally by the PHPS, who will be responsible for receiving indexed files and trial documentation from the investigational site, before forwarding for archiving. Investigational sites must agree to the responsibility of ensuring all contents are indexed before sending to the PHPS. In the case of this trial, PHPS has organised for central archiving to take place on behalf of sites due to the possibility of dental practices changing hands, or being sold during the study archive period.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The University of Liverpool (LCTC and Department of Public Health, Policy and Systems as applicable) undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator site only. The University of Liverpool will archive the documents in compliance with ICH GCP. All eCRFs and trial data will be archived onto an appropriate media for long-term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

# 14 REGULATORY AND ETHICAL CONSIDERATIONS

## Statement of Compliance

The trial will be carried out in accordance with the applicable regulations in the UK.

## Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion.

### 14.1.1 **Informed Consent in an Urgent Care Setting**

Due to the need to provide intervention at the same visit as the patient presenting to the recruiting site for urgent dental care, informed consent must be provided during the same visit. However, patients will be allowed sufficient time to consider the trial prior to consenting and if they are unable to make the decision during the visit then no further follow up for consent will be completed.

## Approvals

The trial protocol, the PISC and all other relevant trial documentation will be submitted for review by the Research Ethics Committee (REC), Health Research Authority (HRA) and University of Liverpool for written approval. All participating sites must be granted NHS permission (or alternative site approval for dental practices) prior to commencing recruitment. A copy of localised versions of the Patient Information and Consent form should be forwarded to LCTC before the centre is initiated and patients recruited.

## Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and ethical e.g. REC requirements, are handled based on their nature and severity.

### 14.1.2 **Non-Serious breaches**

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and PHPS procedures as appropriate. They will be reported to trial oversight committees.

### 14.1.3 **Serious breaches**

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to PHPS who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent Project Steering Committee (PSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the

assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to REC within 7 days by the TM on behalf of the Sponsor and notified to the TMG and PSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, PSC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

# 15 **INDEMNITY**

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical trial. However, the participating site continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the site's duty of care, or any negligence of the part of site's employees. In these cases, clinical negligence indemnification will rest with the participating site.

# 16 PUBLICATION AND DISSEMINATION

## Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Programme Management Group (PMG).

The nature of publications arising from the trial will be discussed at the PMG with named authors identified according to the ICMJE guidelines for authorship (substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work, or revising it critically, for important intellectual content; AND final approval of the version to be published). The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial.

The members of the PSC should be listed with their affiliations in the Acknowledgements / Appendix of the main publication.

### 16.1.1 **Authorship**

Contributors based on ICMJE guidelines for authorship will be included by name at the manuscript head or listed at the end in a by-line as members of the RETURN Consortium which will also be named at the manuscript head.

## Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the REC. The results of the RETURN Main Trial will be published regardless of the magnitude or direction of effect.

Outputs and dissemination of the RETURN programme will be reported in peer reviewed scientific articles, scientific conferences, and to a national conference for stakeholders.

## Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by an internal committee at the PHPS and discussed with the CI in accordance with the PHPS and LCTC policy on data sharing.

# 17 CHRONOLOGY OF PROTOCOL AMENDMENTS

## Version 1.0 (23/10/2020)

Original version submitted as part of the initial Sponsorship Application. This version was never submitted for Research Ethics Committee or HRA approval.

## Version 2.0 (01/12/2020)

| Summary of Amendments from Protocol V1.0 to Protocol V2.0 | | |
|---|---|---|
| **Section No.** | **Section Title** | **Summary of Changes** |
| | Protocol Approval(s) | Wording added to confirm that, due to remote working as a result of the COVID-19 pandemic, protocol approvals have been provided via email instead of wet-ink signature. |
| 3 | Protocol Overview | Self-report added as a measure to a number of secondary objectives.<br><br>Removal of 'phone calls' as the method of follow-up; follow-up may be completed by alternative methods.<br><br>Secondary outcome 9; self-reported follow-up time points added, 6-, 12- and 18-months. |
| 5.3.3 | Impact of COVID-19 | Impact of COVID-19 summary included. |
| 5.4.2 | Secondary Objective(s) | Aligned with the summary of changes above. |
| 9.2 | Secondary Outcomes | Secondary outcome 6; addition of patient self-report as the outcome measure, in addition to the BSA clinical dataset already referenced.<br><br>Table 1; aligned with the summary of changes already listed above. |
| 10.4 | Pre-Randomisation Information Provided by Participant | Section title update; 'Pre-intervention' changed to 'Pre-randomisation' for clarity.<br><br>Prescription information; prescription information of antibiotics and/or analgesics for dental problems to be collected within the last 6 months (previously 3 months). |
| 10.8 | Schedule for Assessments and Follow-Up | Prescription information of antibiotics and/or analgesics for dental problems to be collected within the last 6 months (previously 3 months). |
| 10.8.1 | Follow-Up Schedule – 6 months (26 weeks), 12 months (52 weeks) and 18 months (78 weeks) post-randomisation (+/- 4 weeks) | Self-reported assessments recall periods changed from 3 months to 6 months. |
| 11.10 | Related Adverse Events | Acknowledgement that related adverse events are likely to be reported at 6-, 12- and 18-months to the Central Research Team. Therefore, delays between adverse event onset and reporting to the LCTC are expected. |

## Version 3.0 (26/02/2021)

| Summary of Amendments from Protocol V2.0 to Protocol V3.0 | | |
|---|---|---|
| **Section No.** | **Section Title** | **Summary of Changes** |
| | Title Page | Addition of ISRCTN No and Ethics Ref Number |
| 3 | Protocol Overview | Addition of Secondary objective number 4 ' To identify whether there is a difference between intervention and control groups in attempts to an appointment at a dental practice for planned dental care (as measured by follow up phone calls at 6, 12 and 18 months).' |
| 3.1 | Trial Schematic | Updated trial schematic to accurately reflect protocol wording |
| 5.4.2 | Secondary Objectives | Addition of objective number 4 '4.To identify whether there is a difference between intervention and control groups in attempts to an appointment at a dental practice for planned dental care (as measured by follow up phone calls at 6, 12 and 18 months).' |
| 9.0 | Outcomes | Secondary outcome measures added :<br><br>Secondary outcome 3: Attempts to make an appointment at a dental practice for planned dental care as measured by patient self-report<br><br>Secondary outcome 12: Self-reported attitudes to using planned dental services measured using Protection Motivation questionnaire<br><br>Number 3 to match new objective added<br>Number 12 to answer secondary objective 2 (previously missed off list) |
| 9.0 | Outcomes | TABLE 1- added new objective and outcome accordingly |
| 10.5.3.2 | Emergency Back Up Randomisation Envelopes | Changed wording to accurately represent to back up envelope process. |
| 10.8 | Schedule of Assessments | Added row in schedule of assessments to accurately reflect the text messages and reminders sent to participants. |
| 10.8.1 | | Adding wording about text messages to clarify 'All intervention participants will be sent text message reminders. One will be received within 2 weeks of intervention delivery reminding them of their action plan and goals. The others will be the week before their 6,12 and 18 month follow up and will remind them of the upcoming contact.' |
| 12.3 | Internal Pilot | Section added to reflect the stop/go criteria set for the internal pilot |
| | PROMS | 6 and 12 month TELEPHONE Questionnaire, Page 9 Section 5<br>18 month TELEPHONE Questionnaire, Page 8, Section 4<br>Study documents change to protocol to reflect changes 1- 3 already documented |

| | | |
|---|---|---|
| | | addition of In the last six months have you attempted to make an appointment to see a dentist for routine care (i.e. non-emergency)<br><br>Yes<br>No<br><br>If yes, why have you not been to a dentist: Free text response |
| | PROMS | 6 and 12 month Postal Questionnaire<br>18 month POSTAL Questionnaire<br><br>Study documents change to protocol to reflect changes 1- 3 already documented<br>addition of In the last six months have you attempted to make an appointment to see a dentist for routine care (i.e. non-emergency)<br><br>Yes<br>No<br><br>If yes, why have you not been to a dentist: *Free text response* |
| | PROMS | 6 and 12 month EMAIL Questionnaire<br>18 month EMAIL Questionnaire<br><br>Study documents change to protocol to reflect changes 1- 3 already documented<br>addition of In the last six months have you attempted to make an appointment to see a dentist for routine care (i.e. non-emergency)<br><br>Yes<br>No<br><br>If yes, why have you not been to a dentist: *Free text response* |

## Version 4.0 (08/12/2021)

| Summary of Amendments from Protocol V4.0 to Protocol V5.0 | | |
|---|---|---|
| **Section No.** | **Section Title** | **Summary of Changes** |
| 10.7 | Participant Reimbursement | Addition of payment for staff qualitative interviews of £15 added to schedule. |

## Version 5.0 changes (12/09/2022)

| Summary of Amendments from Protocol V5.0 to Protocol V6.0 | | |
|---|---|---|
| **Section No.** | **Section Title** | **Summary of Changes** |
| 2 | Glossary | Addition of abbreviation |
| 3 | Protocol Overview | Updated addresses and details of contacts as appropriate. |
| 4.5 | Clinical Trials Unit (LCTC) | Amended the LCTC responsibilities to reflect trial management handover to PHPS |
| 4.6 | Department of Public Health Policy and Systems (Central Research Team) | Amended the PHPS responsibilities to reflect trial management handover from LCTC |
| 5.4 | Objectives | Updated objectives to align to the published protocol wording and to clarify timeframes and data streams used more comprehensively |
| 9 | Outcomes | Updated outcomes to align to the published protocol wording and to clarify timeframes and data streams used more comprehensively |
| 10.1.4.5 | Qualitative Trial Components | Added in information about verbal consent for use of audio extracts. |
| 10.8.1.2 | Efficacy Assessments | Removed the inclusion of baseline antibiotic prescriptions (this has been inserted into the protocol in error) |
| 10.8.1.3 | Dental Hospital Data | Removed the inclusion of baseline antibiotic prescriptions (this had been inserted into the protocol in error) |
| 10.9.2 | Participant Discontinuation from Follow Up | Changed wording to reflect trial management handover from LCTC to PHPS |
| 10.9.3 | Complete Withdrawal from Trial | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.2 | Assessment of Seriousness | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.6 | Time Period for Active Monitoring of Safety Events | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.8 | Notification of Deaths | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.9 | Reporting Procedures | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.10 | Related Adverse Events | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.11 | Serious Adverse Events / Related Unexpected Serious Adverse Events | Changed wording to reflect trial management handover from LCTC to PHPS |
| 11.12 | Flowchart for Site/central team Reporting Requirements of Adverse Events | Changed flow chart diagram to better explain reporting procedures for AEs to reflect trial management handover from LCTC to PHPS |
| 11.13 | Investigator (Dentist) and Central Follow-up Team Reporting Responsibilities | Changed wording to reflect trial management handover from LCTC to PHPS |

| | | |
|---|---|---|
| 11.14 | LCTC Responsibilities | Amended the LCTC responsibilities to reflect trial management handover to PHPS |
| 12.7 | Analysis Plan | Updated analysis plan for secondary objective 1 to include some of the secondary outcomes |
| 13.3.1 | Central Monitoring | Changed wording to reflect trial management handover from LCTC to PHPS |
| 13.5 | Confidentiality | Changed wording to reflect trial management handover from LCTC to PHPS |
| 13.7 | Records Retention | Added wording about PHPS centrally archiving site files on behalf of site Investigators |
| 14.4 | Protocol Deviation and Serious Breaches | Changed wording to reflect trial management handover from LCTC to PHPS |
| 16.3 | Data Sharing | Changed wording to reflect trial management handover from LCTC to PHPS |

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# 19 **DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL**

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or Ethical review are submitted as separate version-controlled documents.