The Systemic Response to Periodontal Treatment

The Immune Response after ultrasonic scaling versus hand scaling Periodontal Treatment: A randomised controlled trial

: A randomised controlled trial

Running title: The Immune Response after Periodontal Treatment (IRaPT)

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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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PROTOCOL APPROVAL

The Systemic Response in Periodontal Disease

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TABLE OF CONTENTS

Once protocol draft complete, left click on this section press F9 and update entire table

ABBREVIATIONS

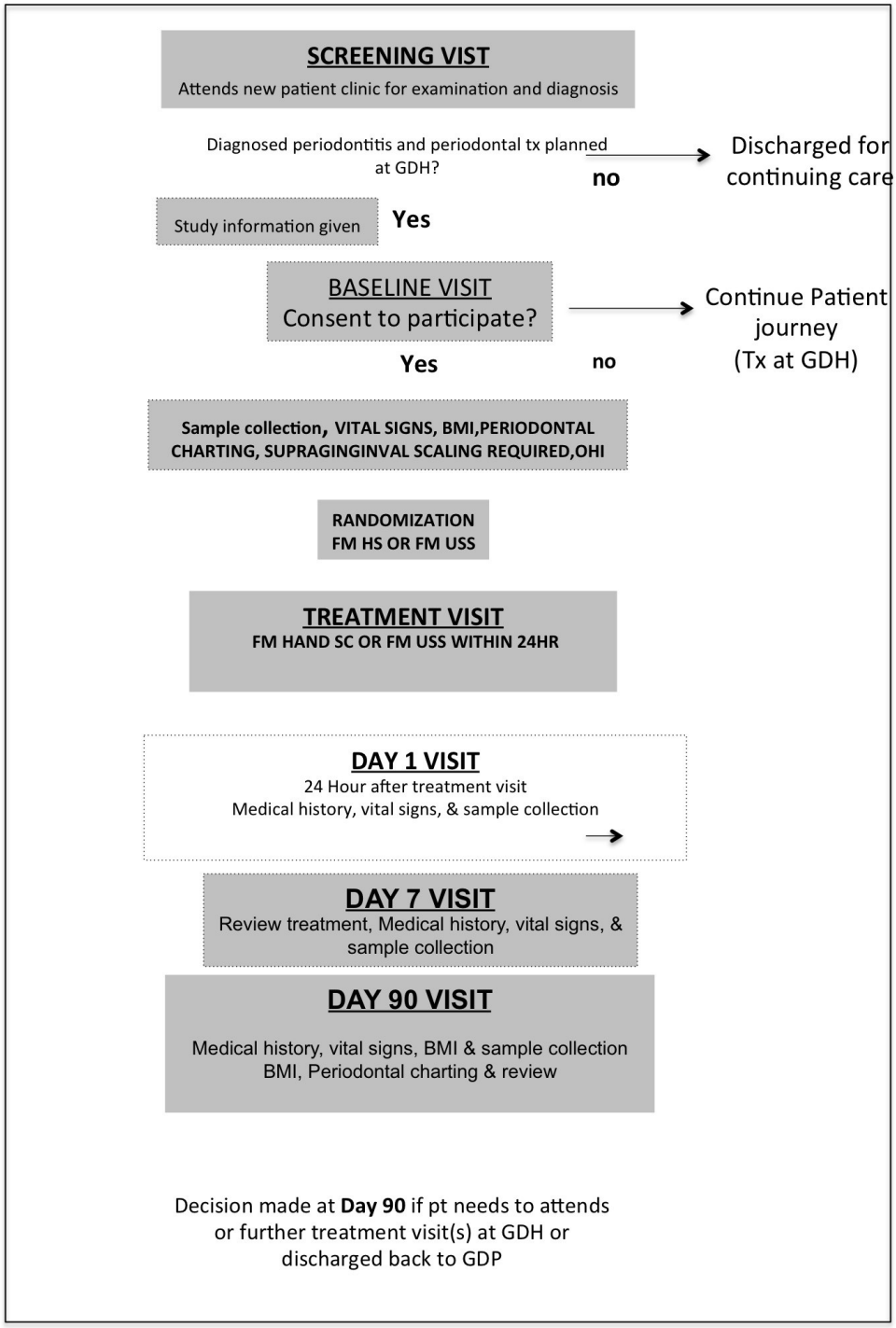
CI	Chief Investigator
CO	Co-Investigator
CRF	Case Report Form
GDHCRF	Glasgow Dental Hospital Clinical Research Facility
PD	Periodontal Disease
PIL	Participant Information Leaflet
R&D	Research and Development
REC	Research Ethics Committee
SD	Standard Deviation
FM	FULL MOUTH
HS	HAND SCALE
USS	ULTRASONIC SCALER

STUDY SYNOPSIS

Title of Study:	**The Immune Response after Periodontal Treatment**
Study Centre:	Glasgow Dental Hospital
Duration of Study:	36 MONTHS
Primary Objective:	To identify changes in systemic markers of inflammation following periodontal treatment, comparing two standard treatment modalities (hands scaling and ultrasonic scaling)
Secondary Objectives:	To investigate bacteraemia, composition and function of oral bacteria, treatment outcomes following periodontal treatment, patient and operator preferences, and treatment time comparing hand scaling and ultrasonic scaling.
Primary Endpoint:	C-reactive protein in the circulation following treatment.
Rationale:	To determine whether hand scaling or ultrasonic scaling are different at inducing a systemic inflammatory response.
Methodology:	RCT
Sample Size:	42 patients (TBC)
Screening:	Patients referred to Glasgow Dental Hospital Unit of Periodontics requiring periodontal treatment at Glasgow Dental Hospital.
Registration/ Randomisation:	Patients and their samples will be assigned a study code. There will be (stratified) randomisation to treatment with either hand scaling or ultrasonic scaling
Main Inclusion Criteria:	• Provision of signed, written, informed consent to participate • Men or women aged 18 years to 70 years inclusive • Periodontal disease requiring treatment at Glasgow Dental Hospital
Main Exclusion Criteria:	• Known or suspected high risk for tuberculosis, hepatitis B or HIV infections • Require interpreter/non English language written material to understand and provide, or any other reason for being unable to provide written, informed consent • History of bleeding diathesis • Females using contraceptive methods. • Pregnant or lactacting females. • Reported diagnosis of any systemic illnesses including cardiovascular, renal, and liver diseases.

	• Any pharmacological treatment within 3 months before the beginning of periodontal treatment. • Specialist Periodontal treatment in the previous 6 months. • Patients who will not tolerate Ultrasonic instrumentation even with local anaesthesia.
Statistical Analysis:	Different types of data will be generated from the study, e.g. - Serum CRP pre and post treatment. - Serum cytokine levels pre and post treatment - Bacteraemia pre and post treatment - Composition and function of oral bacteria pre and post treatment. - Clinical data to provide a measure of severity and extent of periodontal disease pre and post treatment. - Patient centred outcomes of each treatment modality. - See statistical analysis plan (SAP) for further details.

STUDY FLOW CHART



Legend for study flow chart.

Text in **BOLD** indicates a patient visit. Grey shaded boxes indicate stages of the study which fit into the patient journey. All of these would be part of the usual patient journey in the unit of Periodontics.

SCHEDULE OF ASSESSMENTS

Study Procedure	Screening initial consultant appointment	Base line	TREATMENT VISITS	DAY 1 WITHIN 24HR	Day 7 +/- 24HR	Day 90 +/- 10DAY
Study information given	Y					
Review Inclusion/Exclusion Criteria	Y	Y	Y	Y	Y	Y
Obtain initial indication if patient will consider study and appoint for combined study/first treatment visit	Y					
Obtain written consent		Y				
Randomisation		Y				
FMPS & FMBS & Periodontal charting	*	Y				
Blood Collection (8-10am)		y				
blood pressure and BMI record		y				
Medical History	Y	Y	Y	Y	Y	Y
OHI		y	Y		Y	Y
Sample collection (blood, plaque, GCF, saliva)		√		Y	Y	Y
Obtain^/Review consent			Y	Y	Y	Y
Complete CRF		Y	Y	Y	Y	Y

*deepest site on each tooth recorded only

1. INTRODUCTION

1.1 Background

Effective root surface debridement (RSD) is essential for successful periodontal treatment. Myriad studies demonstrate that RSD may be carried out using hand or ulstrasonic instruments with equal efficacy (1). Locally, effective debridement results in reduced inflammation in the gingival tissues, ultimately preserving the dentition. Systemically, RSD results in an immediate inflammatory response with elevated C-reactive protein (CRP), and cytokines (e.g. interleukin-6 and Tumor Necrosis Factor) detectable in the serum (2). This systemic inflammation may relate to systemic dissemination of bacteria from the periodontal pockets into the circulation, during instrumentation. Bacteria are detectable in serum immediately after instrumentation (3). The incidence of the bacteraemia varies considerably between different studies,

ranging from 13% of patients (4) to 43% (5) to 55% (6). These studies used different methods of instrumentation; Kinane et al used full mouth ultrasonic scale, Zhang et al used a mixture of hand and ultrasonic instruments, and Heimdahl et al used curettes only. Whilst tempting to speculate that ultrasonic instrumentation induces less bacteraemia than hand instrumentation, *there is no direct comparison of the effect of ultrasonic instrumentation with hand instrumentation on post treatment systemic inflammation.*

1.2 Rationale

. **We propose that ultrasonic and hand instruments may cause different immediate systemic effects on patients.** The long-term consequences of post-RSD systemic inflammation and bacteraemia are not known. In healthy individuals it could be speculated that the systemic effects of RSD are short lived, resolve, and do not harm the patient. However, in medically compromised patients, for example with vascular disease, such perturbation to systemic homeostasis could be speculated to carry a greater potential risk to health. With an aging population and increased tooth retention, more medically compromised patients receive periodontal treatment.
We propose a study to investigate the systemic impact of different debridement methods, outlined in the diagram below.

1.3 Prior experience of periodontal research

The Chief Investigator (CI) is a specialist periodontist treating patients with advanced and aggressive forms of periodontal disease. The CI has a developing track record in periodontal research, with current research funding in the region of £1.3 million and a number of peer reviewed publications as detailed on attached CV. The CI works in close collaboration with world-renowned immunologists and microbiologists and several consultant periodontist colleagues at the Glasgow Dental Hospital.
DMcK is an extremely experienced Dental Hygienist who also has experience of dental research, including commercial and non-commercial studies, which have included treatment of periodontitis.

1.4 Study hypothesis

There is a difference in the systemic response to periodontal treatment using either hand instruments, as compared with periodontal treatment using ultrasonic instruments.

2. STUDY OBJECTIVES

1. To investigate systemic markers of inflammation following periodontal treatment, comparing two standard treatment modalities (hands scaling and ultrasonic scaling).

2. To investigate bacteremia, composition and function of oral bacteria, treatment outcomes following periodontal treatment, patient and operator preferences, and treatment time comparing hand scaling and ultrasonic scaling.

3. STUDY DESIGN

This Randomized Controlled Trial will be performed according to the Research Governance Framework for Health and Community Care (Second edition, February 2006).

3.1 Study Population

The study will aim to recruit 42 eligible patients requiring periodontal treatment within a recruitment period of 18-24 Months.

3.2 Inclusion criteria

- Written informed consent
- Male or female 18 years to 70 years inclusive
- Periodontal treatment required at Glasgow Dental Hospital or General Dental Practice
- Patients able to travel and attend all study visits.
- Probing pocket depths >5mm on 2 or more teeth at non-adjacent sites with cumulative probing pocket depths of greater than or equal to 40mm (Cumulative probing depth is calculated by evaluating all sites on each tooth. The deepest site on each tooth is recorded and if this value is greater than 4mm this is 'counted' and the sum of all the teeth assessed in this way calculated.)

3.3 Exclusion criteria

- Known or suspected high risk for tuberculosis, hepatitis B or HIV infections
- Require interpreter/non English language written material to understand and provide, or any other reason for being unable to provide written, informed consent
- History of bleeding diathesis
- Pregnant or lactacting females.
- Reported diagnosis of any systemic illnesses including cardiovascular, renal, and liver diseases, and/or regular use of medication to control systemic illness.
- Any pharmacological treatment within 1 month before the beginning of the study, including routine use of any over the counter medications.
- Specialist Periodontal treatment in the previous 6 months.

Randomisation: patients will be stratified according to smoking status then randomized to one of two groups (hand vs ultrasonic) according to the randomization schedule (permuted blocks of size 4 and 6). The randomization schedule will be computer generated and allocation will be concealed up until the point of treatment. Masking: it will not be possible to mask the clinicians providing the treatment; however the researcher collecting the samples and undertaking the analysis will be masked to group allocation, through the use of anonymised coded samples. All other study personnel will not have access to identifiable data.

3.4 Identification of participants and consent

Patients will be identified by the CI or other clinician responsible for the patient. Patients will be screened at this time to establish eligibility. The inclusion/exclusion criteria will be evident from the information taken as part of the normal clinical procedure (eg history, examination and treatment plan). Eligible patients will be initially informed of the existence of the study and approached by the consultant or his/her representative who is treating the patient (E.g. specialist trainee/house officer/GDP/DCP). This initial contact will be to provide the patient with the Participant Information Leaflet (PIL) and establish whether they would consider taking part. At the subsequent visit, (Screening visit), the CI/CO/Registrar/consultant or research nurse will ask whether the patient would like to take part and obtain consent. At each stage, it will be made clear to the patient that that participation is voluntary and they can leave the study at any time without their care being affected.

3.5 Withdrawal of subjects

Patients will be withdrawn for the study if they are no longer eligible (e.g. due to a change in general health) or if the patient withdraws their consent to participate, or if for any other reason the CI or patient's consultant deems it detrimental to the patient to continue to participate. Withdrawal will be immediate. The CI will be informed and will confirm whether the patient wishes any previously obtained samples and associated data withdrawn from the study. The reason for withdrawal and the subsequent action taken will be documented on a case-by-case basis as an addition to the case report form (CRF).

4 Trial procedures

4.1 Study schedule

Patients will attend Glasgow Dental Hospital for screening, baseline, treatment, then Day 1 after treatment, Day 7 after treatment, and review (day 90 after treatment). Screening visits may be undertaken by GDP. The visits are labelled as per the flow chart/table with the purpose of the visit.

Screening visit: New patient assessment

Patients are referred then appointed on a new patient consultant clinic at which a clinical history and clinical examination are completed by the consultant or his/her staff. A treatment plan is then agreed with the patient. If this treatment plan includes periodontal treatment at Glasgow Dental Hospital and the patient is eligible to take part, then the patient will be provided with written and verbal information about the study. The patient will be asked to give an initial indication as to whether they would consider taking part – with emphasis that they should take time to consider the PIL and will have the opportunity to ask further questions, and that their treatment remains unaltered irrespective of their participation. If the patient indicates they would consider participation in the study, they will be appointed jointly to the GDHCRF and the hygienist / registrar (baseline visit).

Baseline visit:

If the patients initially said YES to participating in the study at the screening visit, at this visit, prior to the start of treatment the patient will be asked if they have further considered participation in the study. If yes, consent for sample collection will be sought and samples will be collected by the GDHCRF research nurse and/or dentist/hygienist (the hygienist or dentist will generally only collect plaque samples as s/he will be removing the plaque anyway). This visit includes FMPS & FMBS & Periodontal charting, blood pressure recording, BMI recording and sample collection of GCF, plaque & blood). This visit is also for initial periodontal charting and initial treatment. This visit includes detailed tooth and gum home care instructions and a superficial scaling of the teeth. This is usually carried out by a staff or research hygienist, but may also be undertaken by training grade staff under the supervision of a consultant.
gingival indices will be taken. The patient will then be randomised to full mouth non-surgical periodontal treatment using either hand scalers or ultrasonic instrumentation. Appointments will be make for patient to attend for treatment visits, Day1, Day 7 and Day 90 visits with time in the GDHCRF for sample collection / blood pressure, BMI and periodontal charting where applicable.

Treatment visits - full mouth non-surgical periodontal treatment will be carried out within a 24hr period (+/- 18hr) either using hand instrumentation or ultrasonic instrumentation as per randomization. At the last treatment visit the clinician will verbally enquire whether the patient is happy to continue participation in the study. If yes - then the patient should attend Day 1 (24hrs later (+/- 18hrs) with time in the GDHCRF for sample collection / blood pressure recording.

Day 1 - 24 hours (+/-18hrs) after treatment completed, further samples (GCF/Plaque/blood) and blood pressure recording will be performed. At this visit the clinician will verbally enquire whether the patient is happy to continue participation in the study. If yes - then the patient should attend Day 7 (+/- 1 day) with time in the GDHCRF for sample collection / blood pressure recording, & review of ohi

Day 7 – 7 days after treatment completed, further samples (GCF/Plaque/blood) and tests (blood pressure recording and medical history update) will be performed. At the last treatment visit the hygienist will verbally enquire whether the patient is happy to continue participation in the study. If yes - then the patient should attend the Day 90 visit (+/- 10days) with time in the GDHCRF for sample collection / blood pressure recording, plaque index & review of oral hygiene.

Day 90 - 90 days after treatment (+/- 10 days) Patient appointed jointly to the GDHCRF and for review with consultant or training grade staff / hygienist under consultant supervision. FMPS & FMBS & periodontal charting, medical history, blood pressure recording, BMI & sample collection of GCF/ Plaque / blood will be taken as at baseline, day 1 and day 7 visits.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measure

Changes in serum CRP pre compared with post treatment.

4.2.2 Secondary Outcome Measure

To investigate: ***Secondary Outcomes:***

Microbiome (continuous and discrete data)

- Microbiome analysis of plaque
- Species diversity
- Collected pre intervention (at baseline visit)
- Collected post intervention (at day 1)

Bacteraemia analysis (continuous data)

- Collected simultaneously with serum CRP
    - Day 1, day 7 and day 90 post intervention

Inflammation and immune analysis (continuous data)

- GCF – cytokine measurements
- Serum cytokine measurement
- Serum antibody (anti-bacterial/auto antibody)
- Collected simultaneously with serum CRP
    - Day 1, day 7 and day 90 post intervention

Clinical outcomes (discrete data)

- Periodontal Probing Depths (at day 90 post intervention)
- Loss of attachment (at day 90 post intervention)
- Plaque/gingival indexes
- Blood pressure recording
- Treatment time (time spent on debridement)

Patient centered outcomes (Questionnaire data - qualitative/qu)antitative)

- Patient satisfaction and experience

Clinician centered outcomes – (Interview data - qualitative/quantitative)

- Experience with each instrumentation technique

4.3 Laboratory Tests

The laboratory analysis will be carried out in University research labs using appropriate methodology. The laboratory research group has significant experience in these techniques and works within a large group of research scientists within the University of Glasgow Dental School and Institute for Infection, Immunity and Inflammation – thereby granting access to substantial expertise.

5. STATISTICS AND DATA ANALYSIS

5.1 Statistical analysis plan

Randomized controlled trial to investigate the difference in systemic response to periodontal therapy, using two different treatment modalities – hand instrumentation and ultrasonic instrumentation. Patients will receive one of two interventions – hand instrumentation or ultrasonic instrumentation, as treatment for their periodontal disease. These two interventions will be compared through the following outcomes.

The primary outcome is that of systemic inflammatory response, measured through serum CRP. A variety of secondary outcomes will also be investigated, including clinical outcomes related to periodontal disease; microbiome analysis; inflammation and immune response analysis.

Stratification and Randomization Methods

Our target population is that of patients suffering from periodontal disease.

Randomization to either intervention (hand instrumentation or ultrasonic instrumentation) will be performed using a computerised random number generator (using permuted blocks of size 4 and 6). Patients will be stratified according to smoking status prior to randomization.

Allocation Concealment

Patients will be allocated to each arm of the study by a member of the research team not involved with the clinical delivery of the experimental interventions. Upon attending their treatment appointment, an opaque envelope will contain the allocated intervention arm for the patient. This will be opened immediately before treatment is commenced.

Blinding

Both the patients and clinicians will remain blinded to the intervention until the intervention is carried out. Research personnel will remain blinded to specific patient allocation throughout the process through the means of patient barcodes. The key linking the barcodes to the patients will be available to the Chief Investigator. The intervention codes will only be available once the key analyses have taken place.

Sample Size

The sample size calculation is based on data from previous published studies that measured changes in CRP following periodontal treatment. From these studies a difference of 3.5 mg/l (SD=3 mg/l) in CRP was detected between the two groups receiving different schedules of periodontal treatment (quadrant vs full mouth debrimdement) at primary endpoint. Therefore at 80% power and a 5% significance level, a sample size of n=34 (17 in each group) is required to detect a minimum difference of at least 1 standard deviation (3 mg/l) between the change in CRP levels from baseline to primary endpoint between the two groups (hand vs ultrasonic). To account for potential drop out of 20% we aim to recruit 42 eligible patients to the study.

Study Population

The study will aim to recruit a minimum of 17 patients per group, up to 21 patients per group (to account for drop out) requiring periodontal treatment within a

recruitment period of 18 – 24 Months. The patients will be recruited from new patient clinics in the periodontal department of Glasgow Dental Hospital, Scotland

Statistical Analysis Plan (SAP)

Objectives

To determine if there is a difference in the systemic response to periodontal treatment using either hand instruments, compared to ultrasonic instrumentation.

General Principals

Data will be summarised for patients in both groups. Categorical variables will be summarised with the number of observations and missing values, and number and percentages of patients falling into each category. Continuous variables will be summarised using the number of observations and number missing, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3 respectively), minimum and maximum values. Formal comparisons will be made between the treatment groups using appropriate tests depending on the nature of the data, this may include Chi-Squared tests, Fisher Exact Tests, two sample t-tests and Mann Whitney tests.

Analysis: the effect of treatment group (Manual vs ultrasonic) on changes in CRP levels (and other secondary outcomes):

- Appropriate generalised linear models
- Binary logistic models (for dichotomous outcomes)

Models may be adjusted for age, gender, deprivation levels, operator, smoking, baseline disease levels.

Endpoints

Day 1 post intervention – GCF/plaque/blood samples, blood pressure

Day 7 post intervention – GCF/plaque/blood samples, blood presure

Day 90 post intervention – Full mouth pocket and bleeding scores & periodontal charting, blood pressure, BMI and sample collection (GCF/plaque/blood)

Primary Outcome:

Changes in serum CRP. This will be measured:

- Pre-intervention, at baseline visit (as per flowchart)
- Day 1, day 7 and day 90 post-intervention

Secondary Outcomes:

Microbiome (continuous and discrete data)

- Microbiome analysis of plaque
- Species diversity
- Collected pre intervention (at baseline visit)
- Collected post intervention (at day 1)

Bacteraemia analysis (continuous data)

- Collected simultaneously with serum CRP
    - Day 1, day 7 and day 90 post intervention

Inflammation and immune analysis (continuous data)

- GCF – cytokine measurements
- Serum cytokine measurement
- Serum antibody (anti-bacterial/auto antibody)
- Collected simultaneously with serum CRP
    - Day 1, day 7 and day 90 post intervention

Clinical outcomes (discrete data)

- Periodontal Probing Depths (at day 90 post intervention)
- Loss of attachment (at day 90 post intervention)
- Plaque/gingival indexes
- Blood Pressure
- Treatment time (time spent on debridement)

Current proposal

There is a difference in the systemic response to periodontal treatment using hand instruments, compared to ultrasonic instrumentation.

1.1.1. ADDITIONAL ANALYSES TO THOSE SPECIFIED IN THE STUDY PROPOSAL

Nil

Research questions

Is there a difference in the systemic response to periodontal treatment using either hand instruments, as compared with periodontal treatment using ultrasonic instruments.

Software

All statistical analyses will be carried out with Stata v 16 (or PRISM) or higher versions of these programs.

5.2 Primary efficacy analysis

There is no test intervention therefore no efficacy analysis.

5.3 Secondary efficacy analysis

n/a

5.4 Safety analysis

The safety data (adverse events) – both numbers of subjects and events – will be summarised.

Adverse Event (AE) – any unfavourable and unintended sign, symptom or disease temporally associated with participation in the research project.

Serious Adverse Event (SAE) - An untoward occurrence that:

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation

d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator

Any SAE occurring to a research participant will be reported to the main REC) where in the opinion of the Chief Investigator (CI), the event was:
• "Related" – that is, it resulted from administration of any of the research procedures, and
• "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted to the REC within 15 days of CI becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published on the National Research Ethics Service (NRES) website.

5.5 Software for statistical analysis

All statistical analyses will be carried out with Stata v 16 (or PRISM) or higher versions of these programs

5.6 Management and delivery

S Culshaw and colleagues will manage and analyse study data.

6. STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when the CI deems that one or more of the following situations applies:
OR

i. The planned sample size has been achieved;
ii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;
iii. Recruitment is so poor that completion of the study cannot reasonably be anticipated.

7. DATA HANDLING

7.1 Case Report Forms

Patient data will be collected at the time of sample collection and recorded on the CRF. At the time of sample collection, each sample will be assigned a code, recorded on the CRF. All data associated with analysis of the samples will be collected and stored linked only to the code. The data linking the patient code with the patient data will be stored securely on University of Glasgow Computers, using password protected file encryption. Hard copies will be stored in a locked file at the University of Glasgow Dental School. The data recording sample analysis will include only the patient code and will also be stored on University of Glasgow Computers but will NOT be encrypted. Hard copies of this data will be stored in laboratory record books, kept at the University of Glasgow Dental School. Samples will be stored appropriate to the type of sample, within facilities at the University of Glasgow, with a detailed description of the sample location, use(s) and ultimately disposal, documented in a sample log record. Any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

7.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event reports, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained by the research team for 15 years.

8. TRIAL MANAGEMENT

8.1 Routine management of trial: Trial Management Group

The study will be coordinated from The University of Glasgow Dental Hospital, by the Trial Management Group. The Trial Management Group will include the CI, statistician, research nurse, and laboratory investigators involved in use of clinical samples. The group will monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.
See Data Security Protocol.

9. STUDY AUDIT

Study site-set up visit and site file will be provided once the study has received R & D approval. Study audit visits will be conducted according to NHS Greater Glasgow and Clyde audit processes. Additional visits may be undertaken if required. Investigators and site staff will be notified in advance of any audit visits.

10. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Sponsor and amendment forms will be submitted to the REC and R&D. The CI will liaise with Sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and R&D office.

11. ETHICAL CONSIDERATIONS

11.1 Ethical conduct of the study

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this research study. Patients will only be allowed to enter the study once either they have provided written informed consent.

The CI will be responsible for updating the REC of any new information related to the study.

11.2 Informed consent

Written informed consent should be obtained from each trial participant. Only patients able to consent for themselves will be included in the study. The Consultant or his/her representative, or the Research Nurse will explain the exact nature of the study in writing, provision of patient information sheet, and verbally. This will include the known side-effects that may be experienced, and the risks of participating in this clinical trial. Trial participants will be informed that they are free to withdraw their consent from the study or study treatment at any time, and it will be emphasised to participants that their decision to participate in the study does NOT influence the treatment they will receive in any way.

12. INSURANCE AND INDEMNITY

The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).?

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

13. FUNDING

University of Glasgow Studentship

14. ANNUAL REPORTS

Reports to the sponsor will be coordinated by the university. Annual reports will be submitted to the REC and sponsor with the first submitted one year after the date that all trial related approvals are in place.

15. DISSEMINATION OF FINDINGS

Findings will be presented locally at group meetings, seminars at Glasgow Dental School and at the Institute of Infection, Immunity and Inflammation. In addition, findings will be presented at national and international meetings and submitted to peer review journals. Public engagement in research is important to the investigators and funders. Therefore, outreach activities such as ‘meet the expert’ at Glasgow Science Centre will include findings from these studies and significant findings of broader interest will be promoted with advice and support from the University of Glasgow press office to publicise any key developments and to engage with a wider audience.

16. REFERENCES

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