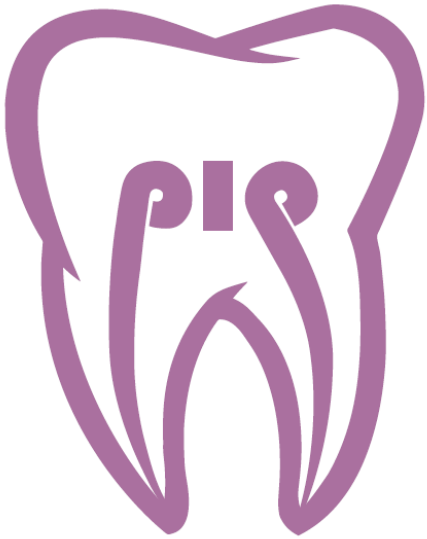
NHS
Health Research Authority



PIP Study Protocols

PIP Feasibility Study

Pulpotomy for the management of Irreversible Pulpitis in mature teeth: V3 01.03.2022

PIP Study

Pulpotomy or root canal treatment for the management of Irreversible Pulpitis in mature teeth: V2 16.05.2023

NHS
Health Research Authority

PIP Feasibility Study Protocol

Pulpotomy for the management of Irreversible Pulpitis in mature teeth

Version 3.0 1 March 2022

PIP Feasibility Study NIHR 129230

GENERAL INFORMATION

RESEARCH REFERENCE NUMBERS

TRIAL REGISTRY NUMBER AND DATE

PROTOCOL VERSION NUMBER AND DATE

OTHER RESEARCH REFERENCE NUMBERS

SPONSOR / CO-SPONSORS / JOINT-SPONSORS

TITLE PAGE

FULL/LONG TITLE OF THE TRIAL
Pulpotomy for the management of irreversible pulpitis in mature teeth (feasibility study)

SHORT TRIAL TITLE / ACRONYM
Pulpotomy for **I**rreversible **P**ulpitis (PIP Feasibility Study)

PROTOCOL VERSION NUMBER AND DATE

Version History	Description of change
Version 1.0 03.02.2021	Submitted to REC
Version 2.127.04.2021	Addition of option for e consent and minor typos amended
Version 3.0 01.03.2022	Administrative amendments for NIHR HTA

PIP Feasibility Study NIHR 129230

RESEARCH REFERENCE NUMBERS

IRAS Number:	289464
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SPONSORS Number:	2.028.20
FUNDERS Number:	NIHR 129230

PIP Feasibility Study NIHR 129230

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

(Optional)

Statistician:

Signature: Date:

..../...../.....

Name: (please print):

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Sponsor	University of Dundee
Funder(s)	This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference 129230). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GDP	General Dental Practitioner
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	Pulpotomy for the management of Irreversible Pulpitis in mature teeth: PIP Feasibility Study	
Trial Acronym	PIP	
Trial Design	The **Feasibility study** will be conducted to assess the clinical and patient feasibility of conducting a pragmatic patient randomised controlled trial.	
Trial Participants	Adult patients (16 years and older) seeking healthcare at NHS general dental practices with symptoms indicative of irreversible pulpitis.	
Planned Sample Size	**Feasibility study:** 10 general dental practitioners each recruiting up to 4 participants.	
Treatment	Full Pulpotomy (FP)	
Follow up duration	Clinical outcomes: 7 days.	
Planned Trial Period	Start date: 01 June 2020 for a duration of 12 months	
Feasibility study outcomes	Objectives: Feasibility objectives: • To identify training needs of GDPs to undertake FP • To develop a clinical training package for study GDPs • To assess if the interventions can be optimally delivered in routine NHS practice • To estimate the number of eligible patients per practice for the main trial • To develop recruitment materials for the main trial accounting for patient and dentist views	Outcome Measures • GDPs recruited in feasibility • successful training in FP technology (on 3D artificial teeth) • clinical fidelity with FP intervention in cohort study • clinical success – patient satisfied with care • potentially eligible patients seen per month

PIP Feasibility Study NIHR 129230

iv. FUNDER

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
National Institute for Health Research HTA Programme	£1,996,749.96

v. TRIAL SPONSOR

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vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee (TSC)
The TSC has a majority independent representation, including the Chair. This group will meet regularly and send reports to the sponsor. Lay members and patient representatives are included.

Janet Clarkson
Paul Coulthard (Chair)
Philip Duncan
Russ Ladwa
Irene Soulsby
Chris Vernazza

Sponsor representative University of Dundee

Data Monitoring (and ethics) Committee (DMEC)
The Data Monitoring Committee members are impartial and not involved in the running of the trial.

Anne Maguire (Chair)
Barbara Chadwick
Rebecca Playle

Trial Management Group (TMG)

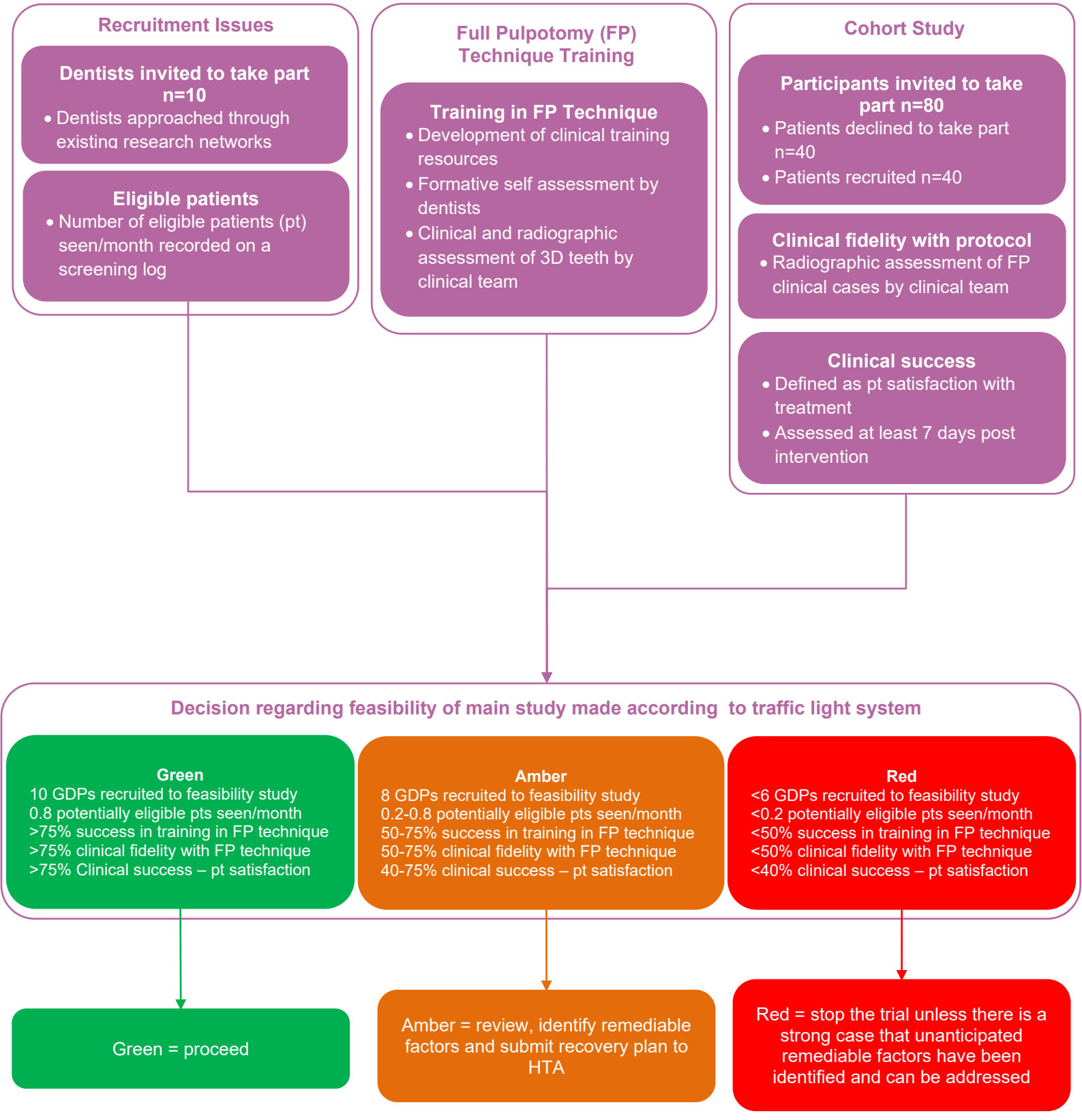
The Trial Management Group meet regularly to ensure all practical details of the trial are progressing and working well and everyone within the trial understands them.

An Operations Management Committee (OMG), will meet weekly in the early stages of the study to ensure smooth running of the trial, troubleshooting issues as they arise, and ensuring consistency of action across the participating centres. A wider Project Management Group (PMG) will meet periodically to monitor the progress of the study.

vii. KEY WORDS:

Full Pulpotomy
Mature Teeth
Irreversible Pulpitis
Randomised Controlled Trial
Dental Primary Care
Severe Tooth Decay
Feasibility Study

viii. FEASIBILITY STUDY DIAGRAM (flow to decision regarding main study)



1 BACKGROUND

The economic burden of dental disease is substantial, accounting for a global expenditure of $544.41bn annually(1). NHS expenditure on dental care in England exceeds £3bn per year and £527 million in Scotland, with over one million patient contacts every week (2). Most of this is due to dental caries, one of the most prevalent non-communicable disease worldwide (3–6). The consequences are cumulative (7,8) and can negatively impact on quality of life and productivity.

1.1 What is the problem being addressed?

Dental caries results in localised and progressive demineralisation of the dental hard tissue; if undisturbed the bacterial insult will cause the pulp of the tooth to become inflamed. Persistent inflammation can lead to *irreversible pulpitis* (when the vital inflamed pulp is incapable of healing) (9), *pulp necrosis* and *abscess* formation.

Preserving the pulp in a healthy state with sustained vitality, preventing apical periodontitis (abscess) and developing minimally invasive biologically based therapies are key themes within contemporary clinical practice. The recent position statement from the European Society of Endodontology (ESE) (10) explains the challenge of managing deep caries and pulp exposure. PIP will investigate outcomes for partial irreversible pulpitis as this is the initial stage of the irreversible damage, confined to the coronal (crown) pulp whilst the radicular (root) pulp remains vital i.e. a healthy blood supply is maintained to the pulp tissue in the roots of the tooth. Removal of the coronal pulp with a ***Full Pulpotomy*** (FP) may keep the radicular pulp vital and thereby avoid the need for complex ***Root Canal Treatment*** (RCTx) or extraction. In this application we will adopt FP as the new technology and recommended by ESE for general practices because a partial Pulpotomy is difficult without magnification (specialist equipment).

2 RATIONALE

Most adults experience decay and the 2009 Adult Dental Health Survey reported that 85% have at least one restoration. Management of dental caries centres around primary prevention and/or operative intervention involving caries removal prior to the irreversible pulpitis stage. If this fails, RCTx involving complete removal of the pulp is the only option (other than extraction) but it is a technically demanding procedure, especially in premolar and molar teeth, and increases patient anxiety (11). It is also time consuming and costly to the NHS and patients. In Scotland, 111,000 RCTxs were provided in 2017/18 costing £8.9m. Approximately 80% of this cost relates to RCTxs on premolar and molar teeth. Extrapolating these figures to England suggests the total cost of this treatment may be in excess of £71m per year.

The PIP team engaged with patients from a general dental practice, patient representatives and the public who highlighted the need to develop more modern dental techniques which aim to preserve rather than remove tooth tissue. This research is important to establish whether FP will, in addition to relieving pain, provide a treatment that is more acceptable for patients, avoiding complex treatment with multiple lengthy visits, possible crowning and a tooth that, if RCTx fails, is frequently extracted and a further fixed or removable prosthetic replacement needed. Therefore, in addition to cost savings, FP may improve patient quality of life through better oral health, fewer episodes of dental pain and possible reduction in dental anxiety.

The recently published commissioning standard in NHS England Restorative Dentistry defined the complexity of clinical and technical procedures according to levels of care 1, 2 and 3 (with increasing complexity). They also reflected the competency of clinicians and the equipment required to deliver care of that level of complexity (12). Complex RCTxs are considered level 2 and 3 and should be referred to specialists or dentists with special interest. The new FP technology could make management of complex cases possible in primary care by GDPs, avoiding the need for extraction or the increase in cost and burden on patients in referral.
FP is a novel technology for NHS primary dental care. Therefore, we are conducting a feasibility study to investigate if it is possible to carry out the FP procedure in primary care, prior to conducting the main trial. The feasibility study will look at the practicalities of providing FP in primary care, as well as assessing training needs of dentists and patient satisfaction with care. Progression to the main trial will be determined against a set of stop/go criteria.

2.1 Why this research is needed now
The importance of this topic to general dental practitioners is clear from the responses to a survey hosted on the Scottish Dental Practice Based Research Network (SDPBRN) website and completed by 168 dentists from across the UK. It indicated that GDPs were very interested in the health technology to be tested in PIP but that clinical training would be required for both FP and RCTx. 91% of responding dentists did not offer Pulpotomy to NHS adult patients and many cited contract restrictions and the costs of bio-ceramic materials as barriers. Overcoming these issues for PIP had already been discussed with UK Chief Dental Officers. Whilst the majority of dentists (97%) offered RCTx for uncomplicated teeth this reduced to 68% and 20% for teeth with a moderate or complex risk of adverse outcomes indicating case selection will be required in PIP. Respondents confirmed our preliminary finding from analysis of tooth-specific data from NHS Scotland national datasets that around 15% of root treated teeth required re-intervention with repeat RCTx, surgical endodontics or extraction at 1 year.

Systematic reviews and randomised controlled trials suggest that Pulpotomy may offer comparable treatment success rates and might be a cost-effective alternative to RCTx, but the evidence base is weak and sparse for the management of vital mature teeth with clinical signs of irreversible pulpitis in the UK NHS (13–16). Two randomised controlled trials conducted in an adult population reported a success rate of Pulpotomy comparable to RCTx (97.6% v 98.3% at 1 year) (17); 85% v 87.5% at 18 months (18). However, both trials were conducted outside of the UK and in the secondary care setting. These studies have limited generalisability due to lack of methodological rigor, difference in the health systems and the clinical approaches used. There is one ongoing trial in the UK (19) looking at this research question in a secondary care setting. The chief investigators of the ongoing study are co-applicants on this proposal.

RCTx success rates vary considerably in the literature. A systematic review (20) together with recent studies conducted internationally (21–23), including primary and secondary care, concluded that the 2- to 10-year survival outcomes of RCTx ranged from 72% to 94.4%. Treatment success rates in primary care dentistry in Sweden, according to periapical status, was 62% immediately after treatment (24); however, a review on RCTx survival in General Dental Services in England and Wales estimated 74% of root canal treated teeth pass through 10 years without re-treatment, apical surgery or extraction and the survival rate was

above 90% in the first year (22). Evidence from a systematic review and a retrospective follow-up study suggests that the success rate of Pulpotomy for permanent posterior teeth may be over 90% at one-year follow-up, but the participants in the included studies were not representative of UK NHS practice (13,25).

Our PPI work has included interviews with patients attending for dental treatment and discussion at a patient forum. It found that patients would value alternative treatment to avoid RCTx, be willing to undergo a FP, be randomised to that or RCTx and outcomes important to them have been included.

2.2 COVID-19

The COVID-19 pandemic has had a significant impact on the provision of dental care. Primary care settings were forced to close in March 2020 as part of the UK nationwide “lockdown”, which has impacted on and caused a backlog in patient care. Although elements of NHS dentistry are starting up again, this is against a backdrop of ever changing COVID-19 restrictions. These are challenging times for dentists. There is a heightened demand for dental care due to the restricted access to treatment, yet there are also continued limitations to the volume of patients that can be seen daily.

RCTx is commonly completed over a number of visits as it is a technically challenging procedure. FP treatment is usually completed in a single visit. This means FP could have a positive impact in reducing the number and duration of patient contacts within a dental practice. In addition, the volume and therefore cost of personal protective equipment required to treat irreversible pulpitis per patient would be significantly reduced with a full pulpotomy treatment, compared to a multi-visit root canal treatment.

There are many uncertainties in the post-acute COVID-19 pandemic era, however it is likely that aerosol generating procedures (AGPs) should be carried out sparingly in order to prevent transmission of the virus. The PIP feasibility study and trial can be considered as even more pertinent in a post-acute COVID-19 age as it not only has the potential to inform new minimally invasive treatments for irreversible pulpitis, but also to inform clinical aerosol reduction practices.

3 AIM, OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS OF THE FEASIBILITY STUDY

Aim: To assess the feasibility of conducting a trial of the clinical and cost-effectiveness of FP as compared to RCTx for mature pre/molar teeth in adults with symptoms indicative of irreversible pulpitis.

3.1 Primary objectives

Feasibility study objectives:

- To identify training needs of GDPs to undertake FP
- To develop a clinical training package for study GDPs
- To assess if the intervention can be optimally delivered in routine NHS practice

- To estimate the number of eligible patients per practice for the main trial
- To develop recruitment materials for the main trial accounting for patient and dentist views

3.2 Primary endpoint/outcome

- GDPs recruited in feasibility
- successful training in FP technology (on 3D artificial teeth)
- clinical fidelity with FP intervention in cohort study
- clinical success – patient satisfied with care
- 0.8 potentially eligible patients seen per month

4 TRIAL DESIGN

The feasibility study has been designed to determine progression to a pragmatic, primary dental care, multi-centre, two-arm patient randomised control trial with an internal pilot comparing the clinical and cost effectiveness of FP compared to RCTx in pre/molar teeth of adults 16 years and older showing signs indicative of irreversible pulpitis. The PIP feasibility study design has benefited from considerable active and informative input from patients in general dental practice, the HSRU public involvement group, and a national survey of GDP's and practitioners with research experience.

The inaugural meeting of the NIHR HTA SCRIPT Trial (17/127) provided the opportunity for the multidisciplinary research team, research partner BUPA, research experienced general dental practitioners, PPI collaborators and BDA representative to contribute to the co-design of the PIP feasibility study and trial.

4.1 Health Technology being assessed in the Feasibility study

Health Technologies: Developed and delivered by PIP clinical experts who will:

- Ensure study dentists understand and appreciate the scientific and clinical rationale for PIP
- Present the latest evidence and international recommendations in diagnosing the pulpal inflammatory state and taking diagnostically acceptable periapical radiographs
- Provide practical guidance using standardised clinical images, instrumentation techniques and use of materials.

Full Pulpotomy Procedure:

- Pre-operative peri-apical radiograph
- Access cavity preparation
- Where caries removal is necessary, this should be complete and carried out in a systematic way removing it completely at the periphery of the cavity then progressively

over the pulp, for controlled reduction in the bacterial load preventing further bacterial contamination of the pulp

- Once the pulp has been reached a new sterile bur should be used with water coolant to remove pulp to the level of the radicular/root canal orifices.
- Haemostasis (within 5 minutes) and disinfection should be achieved with cotton pellets soaked with 5% sodium hypochlorite under rubber dam isolation.
- If haemostasis cannot be achieved after 5 minutes the tooth should undergo pulpectomy and RCTx as per the clinician's normal practice
- Once haemostasis has been achieved for all root canals (all root canals have to be vital i.e. bleeding stopped), a hydraulic calcium silicate cement should be place directly onto the pulp tissue
- Immediate post-operative radiograph for FP after placement of definitive restoration. This radiograph will be used to confirm fidelity of theprocedure. To confirm adequate coverage and thickness to floor of chamber and pulp stumps and absence of porosity and the tooth definitively sealed immediately to prevent micro-leakage.

Clinical fidelity to the protocol will be assessed by the study's clinical team. The clinical team will use the criteria below to evaluate post-operative radiographs uploaded to the trial website by the participating dentists. Ultimately the decision as to whether fidelity with the protocol has been maintained is a clinical judgement, made by the clinical team.

Clinical fidelity criteria

- Access cavity preparation (complete removal of the pulp chamber roof).
- Adaption of the Biodentine material (covers the floor or pulp stumps, adequate thickness of 2mm, no porosity)
- Adequate final restoration (no excess Biodentine on walls preventing peripheral seal).

4.2 Clinical Training

Our preparation for PIP confirmed the need for and importance of effective clinical training. Training will be provided over two sessions. One session will be a remote training session in which all dentists recruited to the feasibility study will receive training in the background and evidence for FP, along with theoretical training in the FP technique. The next session will be a face to face training session at each clinical centre. For the dentists in each clinical area We will confirm and identify the training needs of GDPs to inform development of the training package for the full trial. PPI members will be invited to the training event to contribute to discussions of training and recruitment.

As FP will be a new technology to most participants, instruction will demonstrate the procedure and establish the standard level of care. Instruction in access cavity preparation and choice of materials will include a hydraulic calcium silicate cement (e.g. Biodentine). 3D printed artificial teeth (see Figure 1 below) are routinely used for RCTx training but their use in training in FP techniques and success assessment is novel. We estimate 4 teeth for each dentist will be sufficient for them to feel confident and competent in the technique.

Formative assessment for the dentists will include self-assessment using a success checklist that measures success against the FP training criteria below. Success in training will be determined using the FP training criteria below to evaluate the full pulpotomy procedures carried out on the 3D teeth and assessment of post-operative radiographs taken of the 3D teeth. Ultimately the decision as to whether a dentist has been successfully trained in the full pulpotomy technique is a clinical judgement made by the study's clinical team.

FP Training criteria:

- Access cavity preparation (complete removal of the pulp chamber roof).
- Adaption of the Biodentine material (covers the floor or pulp stumps, adequate thickness of 2mm, no porosity)
- Adequate final restoration (no excess Biodentine on walls preventing peripheral seal).

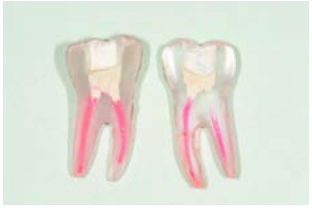


Figure 1 – Example of sectioned Endo reality 3D tooth showing FP

4.3 Study process training

Study process training will be delivered by non-clinical members of the PIP team who will:

- Provide an introduction of the study design and overview of the protocol.
- Present practical guidance on the feasibility process including consent, data collection, study paperwork and e-recording.
- Provide training in Good Clinical Practice necessary for the feasibility study.

4.4. Population

Following successful completion of the clinical training, dentists will be asked to recruit 4 patients seeking NHS healthcare at their dental practice.
The eligibility of all participants will be assessed and determined by their dentist following clinical and radiographic examination.

- Inclusion Criteria
  - Adults (16 years and over) with symptoms indicative of irreversible pulpitis [as defined by ESE (10)] in a pre/molar tooth with deep caries and or a deep restoration.
- Exclusion Criteria
  - Tooth with immature roots, clinical or radiographic signs of a necrotic pulp, or a poor prognosis (e.g. internal or external resorption).
  - Presence of a sinus, tenderness to percussion, buccal tenderness, pathological mobility or evidence of pathology on a periapical radiograph.

- Insufficient tooth tissue for a restoration
- All treatment delivered under a private contract.
- Unable to give informed consent

4.5 Patient Participant process

The dentist will explain the study to the patient. The patient will be given an information pack including the Participant Information Sheet and will have time to digest this information and ask any questions they may have.

If a patient agrees to take part, they will be asked to complete a consent form. Once the consent form is signed, the recruited participant will be allocated a study ID number that will be used on all trial documentation.

Each recruited participant will be offered the Full Pulpotomy treatment in the first instance. Feedback from PPI groups and dentists indicates FP will be the preferred treatment. Should the dentist feel another treatment is more appropriate they will proceed as they decide. Should a recruited participant change their mind and not want a Full Pulpotomy, the dentist will follow the course of treatment the participant requests.

Following their Full Pulpotomy treatment, participants will be given a 'What's Next' document. This will outline the next steps and will also include a £15 voucher to thank them for taking part in the feasibility study.

Participants will be contacted by their preferred method (email, text message or phone call) by the trial office at least 7 days post intervention to give feedback on satisfaction with care.

All participants will be invited to take part in a Qualitative Interview and details of this will be included in the 'what's next' information. Participants will consent to a Qualitative Interview via an optional statement on the feasibility study consent form.

If the participant "opts in" to take part in a Qualitative Interview, their second £15 thank you voucher will be sent to them after their interview has taken place. If the participant does not opt in for the Qualitative Interview element, the voucher will be posted to them after they have given feedback about their satisfaction with care.

After the initial intervention participants will receive any treatment deemed clinically appropriate by their dentist as per normal practice.

4.6 Qualitative interviews

Qualitative research can make an important contribution to feasibility studies (26). Qualitative interviews will be conducted with dentists and patient participants who have taken part in the feasibility study to explore the appropriateness of the training, the feasibility of delivering the interventions and recruitment of participants to the trial. These will also contribute to the design of the trial recruitment strategies. At least one dentist from each practice will be invited to interviews. All patient participants will be invited to take part in a qualitative interview. Interviews with dentists will be guided by the Theoretical Domains Framework (27). Interviews

with patient participants will be informed by the Theoretical Framework of Acceptability (28). Interviews will be audio-recorded and transcribed verbatim. The data will be analysed using framework analysis (29).

4.7 Feasibility criteria

The progression criteria will be assessed based on traffic light system of green (proceed), amber (review, identify remediable factors and submit recovery plan to HTA) and red (stop) as follows:

Green: - automatic progression. - Amber: - identify remediable factors and submit recovery plan to the funder with new targets for the following 6 months. - Red: - stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed.

Feasibility criteria – assessed at month 13	Green	Amber	Red
Number of GDPs recruited in feasibility study	10	8	<6
Success on training in full pulpotomy with 3D teeth	>75%	50-75%	<50%
Clinical fidelity with FP intervention in cohort study	>75%	50-75%	<50%
Clinical success – participants satisfied with care	>75%	40-75%	<40%
Number of potentially eligible patients seen per month per GDP	0.8	0.2-0.8	<0.2

5 TRIAL SETTING

This is a multicentre feasibility study set in primary dental care. Dentists (GDPs) will be recruited from ten primary dental care practices from UK regions with established research networks and experience of collaboration (Scotland and England). All GDPs approached and expressing interest will be asked to complete a site initiation questionnaire for their dental practice.

6 PARTICIPANT ELIGIBILITY CRITERIA

The eligibility of all participants will be assessed and determined by their dentist following clinical and radiographic examination.

6.1 Inclusion criteria feasibility study

- Adults (16 years and older) with symptoms indicative of irreversible pulpitis [as defined by ESE (10)] in a pre/molar tooth with deep caries and or a deep restoration.

6.2 Exclusion criteria feasibility study

- Tooth with immature roots, clinical or radiographic signs of a necrotic pulp, or a poor prognosis (e.g. internal or external resorption).
- Presence of a sinus, tenderness to percussion, buccal tenderness, pathological mobility or evidence of pathology on a periapical radiograph.
- Insufficient tooth tissue for a restoration
- All treatment delivered under a private contract.
- Unable to give informed consent

7 TRIAL PROCEDURES

The PIP trial team have considerable experience of recruiting to NIHR HTA trials in dental primary care and lessons learned will be applied to ensure predictable recruitment and retention.

7.1 Recruitment

7.1.1 Recruitment of practices

General dental practice is the main provider of NHS dental care. We aim to recruit 10 GDPs with research experience from across the UK via our partner research networks and dentists who may or may not be active in other dental trials. Working with research ready and experienced dentists will help us speedily identify training needs, service requirements and criteria for successful intervention delivery. A list of participating practices will be kept up to date and provided on the public trial website: https://w3.abdn.ac.uk/hsru/pip.

The PIP feasibility study will benefit from recruitment efficiencies gained through the NIHR HTA SCRIPT Trial which has the same CI's from the University of Dundee and Aberdeen and the established networks formed as a result of successfully undertaking multiple large scale NIHR HTA trials in general dental practice. Recruitment will be open to all NHS general dental practices in the participating regions. Practices that have successfully recruited to and delivered previous dental HTA trials will be targeted through our partner research networks.

Following the expression of interest, an appraisal of each practice's ability to recruit participants will be conducted including evidence of a sufficient supply of eligible patients from their routine patient base or new patient population. This will include a request for evidence of providing RCTx for pre/molar teeth from practice management systems or routine data. Digital X-ray facilities at the practice will be preferred but are not essential.

7.1.2 Recruitment of participants

Trial dentists will identify patients presenting at their clinic/practice with symptoms indicative of irreversible pulpitis who meet the inclusion criteria and explain the trial. Patients with these symptoms who contact the practice by telephone will be informed the trial is taking place by the practice receptionist. Potentially eligible patients who express interest will be given a participant information leaflet (PIL) and an appointment will be arranged for their treatment as per current clinical practice. In the event that a patient presents at an appointment requiring immediate treatment, sufficient time to make an informed decision regarding willingness to participate will be given. At the treatment visit the patient will be given the opportunity to clarify any questions prior to written consent being obtained.

7.1.4 Screening

A screening log will be completed to provide information on the frequency of potential cases, acceptability of the new treatment FP and willingness to be randomised.

7.1.5 Thank you vouchers
Participants will receive £30 in high-street vouchers as a thank you for participating in the trial – £15 following recruitment and £15 at the end of follow-up. This will be given to them by a member of the dental or trial team following the participant's initial treatment visit.

7.2 Consent
Informed consent to participate in the feasibility study will be sought and obtained according to GCP guidelines. When attending an emergency or routine visit at their dental practice, potentially eligible participants will be given a PIL detailing the study process and the FP procedure, including the risks and benefits of FP. Informed signed consent will be sought either at that visit or a subsequent treatment visit after sufficient time for the participant to accept or decline involvement and obtained using a standardised consent form by the participant's clinician who will be appropriately trained. Participants will be free to withdraw consent at any time. The participating clinicians will verbally reiterate the information contained in the information sheet and answer any questions that patients may have about the trial as part of the informed consent process. The participants will be asked to consent to: participation; follow up; contact to invite them to take part in a qualitative interview about their experience in the study; contact in the future about this and other relevant research; electronic tracing using NHS data (and if relevant BUPA data); and data linkage with routine NHS data sources.

7.2.1 Obtaining e-Consent
To cater for participant preference and COVID adaptations at local dental practices, participants may opt to consent using an e-consent form via the secure web-based trial management system hosted by CHaRT. If this option is preferred, potentially eligible participants will be asked during screening to provide their email address which will be entered into the secure web-based trial management system by the dental practice staff. Participants will be sent an email from the secure website with a link to verify their email address. When their email address is verified, participants will be automatically emailed the PIL and a link to the participant e-consent form for their unique study number. The e-consent form will be identical to the approved paper version of consent form, with the approved PIL version number and date automatically populated. The participant will be asked to provide their signature online via a signature box using a finger tracing via a touch screen or using a mouse. Should participants prefer to use e-consent this may be provided at any time prior to the treatment visit or on the day of treatment. Clinician counter-signature will be recorded on the e-consent only after discussion has taken place with the participant about the study and any questions have been answered. Any e-consent obtained will be verbally confirmed by the site at the treatment visit. Participants will be sent a copy of the e-consent form for their own records and a copy will be retained in the investigator site file and TMF.
The email address of potentially eligible participants who are sent the study information and decline to take part will be deleted from the trial management system after 3 months.
The trial management system used to record e-consent has a clear audit trail with tracking of all inserts or updates made, database interactions logged against a user and date/time and the audit trail can be downloaded and analysed at any time by authorised users.

7.3 Randomisation
As the feasibility study aims to determine if the intervention can be carried out in primary care, all participants will receive a full pulpotomy and there will be no randomisation. Randomisation will however take place in the main trial. The views and opinions of the dentists taking part in the feasibility will be taken into consideration when developing the systems and processes.

7.4 Blinding
No blinding will be carried out during the feasibility study. Operator and participant will not be blind to the intervention.

7.5 Emergency Unblinding
Not applicable.

7.6 Baseline data
Age and gender will be recorded on the participant details form.

7.7 Feasibility study assessments
7.7.1 Clinical Outcomes
Clinical fidelity to the technique will be monitored by assessment of post-op radiographs by the study team.

Clinical success will be determined by patients satisfaction with treatment using a question adapted from the Patient Reported Experience Measures (PREMs) outlined in the NHS England Guide of Commissioning Dental Specialties (30). The question is based on a scale ranging from not satisfied to completely satisfied. The intervention will be considered successful if the patient is somewhat to completely satisfied with their treatment. Participants will be contacted by their preferred method by the trial office from day 7 to feedback on satisfaction with care, experience and symptoms.

7.7.3 Health Economic Outcomes
We will not collect health economic data during the feasibility study.

7.7.4 Feasibility Monitoring/reassurance
Experienced co-design of PIP confirmed the benefit for dentists of monitoring and feedback. After each feasibility participant treatment visit a member of the clinical research team will contact the dentist. Examination of pre- and post-operative radiographs by the clinical research team will identify issues of case selection and success of the technology according to the criteria of success in the training session. This will provide the opportunity for confirmation of checklist and success criteria, identifying supplementary training needs and/or reassurance if required.

7.8 Qualitative interviews
Qualitative interviews will be conducted with dentists and patient participants who have taken part in the feasibility study to explore the appropriateness of the training, the feasibility of delivering the interventions and recruitment of participants to the trial. These will also contribute to the design of the trial recruitment strategies.

For patient participants the qualitative interview will be part of the feasibility study and patient participants will have the option to consent to the interview as part of consenting to the feasibility study. If a patient participant gives their consent, a suitable date and time for a remote qualitative interview will be arranged after their follow up questionnaire has been completed. The interview will be conducted by an experienced researcher and audio recorded.

All dentists will be invited to take part in an interview. Dentists will be contacted directly by the qualitative research team, informed about the qualitative study and invited to take part in a remote interview at a convenient time. Dentists will be contacted and interviewed at one of three time points: shortly after training, after recruiting 1 – 2 participants or after recruiting 3 – 4 participants in order to capture a range of experiences. Dentists will be asked to consent to take part in an interview.

The interviews will be guided by topic guides developed from the literature and other dental trials. The topic guide for dentists will be guided by the Theoretical Domains Framework (27) and focus on training, delivering the intervention, acceptability of the intervention and recruitment. The topic guide for patient participants will be informed by the Theoretical Framework of Acceptability (28) and focus on experiences of recruitment and intervention, and acceptability of the intervention. Interviews will be audio-recorded and transcribed verbatim. The data will be analysed using framework analysis (29). The framework analysis will involve the following stages: identifying initial themes, labelling the data, sorting the data by theme and synthesising the data. The interviews will be conducted by an experienced research associate who will also lead the data analysis. As the analysis progresses regular meetings will be held with the research team to discuss the emergent themes and consider the implications of the results for the main trial.

7.9 Withdrawal criteria/ change of status

Participants remain in the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status, with the exception of complete withdrawal of consent, means the participant will still be followed up for all trial outcomes wherever possible. All data collected through the screening log up to the point of complete withdrawal may be retained and used in the assessment of the feasibility study outcomes.

7.10 End of feasibility study

Feasibility criteria

The progression criterial will be assessed based on traffic light system of green (proceed), amber (review, identify remediable factors and submit recovery plan to HTA) and red (stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed) as follows:

Feasibility Criteria	**Green**	**Amber**	**Red**
Number of GDPs recruited in feasibility	10	8	<6
Success of training in FP technology (3D artificial teeth)	>75%	50-75%	<50%
Clinical fidelity with FP intervention in cohort study	>75%	50-75%	<50%
Clinical success – participant satisfied with care	>75%	40-75%	<40%

Number of potentially eligible patients seen per month per GDP	0.8	0.2-0.8	<0.2

The feasibility study will end at month 12 (June 2021) and will coincide with the stop/go criteria evaluation to determine if progression to the main study is possible.

The end of follow-up for each feasibility participant is defined as the final data capture on that individual. This may vary depending on the time point at which they are recruited into the feasibility study.

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

A summary report of the feasibility will be provided to the funder, Sponsor and REC with a decision regarding whether or not to proceed to full trial.

8 ADVERSE EVENTS

8.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with trial participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect Or is otherwise considered serious by the treating clinician (PI)

Within the PIP feasibility study only adverse events (AEs) and Serious Adverse Events (SAEs) that has a reasonable causal relationship to the full pulpotomy treatment in the study tooth will be recorded.

8.2 Adverse events

Whilst a full pulpotomy is a novel treatment in NHS primary care clinical practice, in terms of clinical procedure it is more conservative than the established root canal treatment and could be considered as the same technique that is used in the initial stage of a root canal treatment. We don't anticipate any safety concerns with this treatment. The dentists taking part in the feasibility study will be fully trained in the FP technique and patients will receive the usual standard of care treatment from their dentist during and following the intervention as normal.

The following adverse events are not common but potentially expected:

- Further failure of tooth vitality with associated signs or symptoms (e.g. pain, infection, swelling, periodontitis)
- Failure due to peri-radicular pathology with associated signs or symptoms (e.g. pain, infection, swelling, periodontitis)
- Dental infection associated with the feasibility study tooth
- Further treatment required (under local anaesthetic and/or general anaesthetic)
- Perforation
- Hypochlorite leakage into the oral cavity
- Hypochlorite injury

8.3 Recording and reporting of SAEs

8.3.1 Detecting SAEs

SAEs will be recorded from the time a participant consents to join the study until the end of their follow up. Events that are serious but are not related to full pulpotomy in the trial tooth

will not be recorded as SAEs. Elective admissions and hospitalisations for treatment planned *prior to* trial intervention, where appropriate, will not be considered as an SAE.

8.3.2 Recording SAEs
Once causality has been evaluated, SAEs will be captured on an SAE form. In addition, death for any cause (related or otherwise) is recorded on the SAE form.

8.3.3 Evaluating SAEs
Seriousness, causality and expectedness should be evaluated.

Assessment of Seriousness
The local investigator (PI) should make an assessment of seriousness as defined in Section 8.1.

Assessment of Causality
Each SAE should be clinically assessed for causality based on information available and reviewed as new information becomes available. i.e. relationship of SAE to the trial intervention. All SAEs judged as having a reasonable suspected causal relationship to the trial intervention will be considered as SAEs.
Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness
When assessing expectedness refer to the expected events (Section 8.2).

8.3.4 Reporting SAEs
Reporting responsibilities of the PI
It is the responsibility of the Principal Investigator (PI) dentist to check for AEs when participants attend for treatment / follow-up.

- Using medical judgement in assigning seriousness, causality and providing an opinion on whether the event was anticipated
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs are recorded and reported to the sponsor in line with the requirements of the protocol.

Reporting responsibilities of the CI
To report an SAE to the Trial Office, the Investigator can either complete a hard copy of the SAE form and email or fax it to the Trial Office or complete the SAE form on the study website. If the SAE form is completed on the study website the trial manager will be automatically notified. If, in the opinion of the PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the Sponsor within 24 hours of receiving the signed SAE notification. The Sponsor will delegate assessment of

SAEs to the CI. If the CI judges an event to be a SUSAR then she will report it accordingly. The Sponsor cannot downgrade an assessment from the PI or CI. If the CI wishes to downgrade an assessment from the PI, the PI's agreement to the revised assessment must be obtained and the discussion documented. Any disparity will be resolved by further discussion between these parties – the discussion will be documented.
If all the required information is not available at the time of reporting, the CI must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size

Since this is a feasibility study and its aim is not to estimate a treatment effect, a sample size calculation was not performed. We aim to recruit 10 dentists and 40 patients because it was considered a large enough sample to inform training needs and recruitment to the main trial

9.2 Planned recruitment

We are aiming to recruit 10 dentists by the end of month 11 and up to 40 patients by month 11.

9.3 Statistical analysis plan

Demographic baseline characteristics and feasibility outcomes will be summarised by centre if applicable and using appropriate descriptive statistics.

9.3.1 Summary of baseline data and flow of patients

Baseline data will be summarised as described in section 9.3. The feasibility flow of participants will be presented as a diagram following adapted recommendations from the CONSORT extension for feasibility and pilot trials. (ref: https://www.bmj.com/content/bmj/355/bmj.i5239.full.pdf)

9.3.2 Primary outcome analysis

Not applicable for feasibility study

9.3.3 Secondary outcome analysis

Not applicable for feasibility study

9.4 Subgroup analyses

Not applicable for feasibility study

9.5 Adjusted analysis

Not applicable for feasibility study

9.6 Interim analysis and criteria for the premature termination of the trial
There are no planned interim analysis.

9.7 Participant population
Adults with symptoms indicative of irreversible pulpitis [as defined by ESE (10)] in a pre/molar tooth with deep caries and or a deep restoration.

9.8 Procedure(s) to account for missing or spurious data
For the primary analysis, we will explore patterns of missing data and consider how robust the findings are using multiple imputation approaches under an assumption of missing at random, and pattern mixture models.

9.9 Other statistical considerations.
Methods to protect against other sources of bias

Performance bias will be minimised by monitoring fidelity with the clinical protocol. Early assessment of pre- and post-op radiographs by a clinical assessor will enable monitoring of technique This will provide the opportunity for feedback if necessary and further training.

Assessment bias will be minimised by radiographic success being determined by an independent clinical assessment panel comprising of the clinical co-applicants.

9.10 Economic evaluation
No economic evaluation will be carried out during the feasibility study

10 DATA MANAGEMENT

10.1 Data collection tools
An anonymised screening log has been created for the purposes of the PIP feasibility study data collection. No participant identifiable data will be recorded.

10.2 Data handling and record keeping
Screening log data will be either be entered into the database by the designated team members working in each site or sent to the Trial Office for entry into the database depending on practice circumstances. Staff in the Trial Office will work closely with the team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks by the Trial Office will further enhance the quality of the data.

10.3 Retention of data
Personal data will not be retained any longer than is required for the purpose for which they have been collected and will be stored in compliance with the sponsor's standard operating procedures. We will explore long term follow of the whole cohort of participants. Documents will be reviewed by the CIs before being destroyed. We plan to seek consent to allow collection of long-term data on restoration longevity and health resource usage.

10.4 Access to Data

The CI, PIs and all institutions involved in the trial will permit trial related monitoring, audits, and REC review. The CI agree to allow the Sponsor or, representatives of the Sponsor, direct access to all trial records and source documentation.

10.5 Archiving

The Sponsor is responsible for ensuring that trial data is archived appropriately. All essential data and documents (electronic and hard copy) are retained for a period of at least 10 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs.

11 MONITORING, AUDIT & INSPECTION

11.1 Project management

University of Dundee will sponsor the trial. An independent Trial Steering Committee (TSC) and an independent Data Monitoring and Ethics Committee (DMC) have been convened.

The role of the TSC is to monitor and supervise the progress of the trial. The TSC membership consists of an independent Chair and other independent members, two PPI representatives and the Co-Chief Investigators (CI). The NIHR HTA will be invited to nominate a representative to sit on the TSC. Other members include the grant holders. Observers may also attend, as may other members of the Project Management Group (PMG) or members of other professional bodies at the invitation of the Chair.

The DMC is independent of the TSC and trial co-applicants. It will monitor accumulating feasibility study data during the course of the trial and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the feasibility study. It is anticipated that both TSC and DMC will meet at least annually during the feasibility study and will continue to meet at least annually if the feasibility study progresses to the main study. The CIs, all PIs, study co-ordinators, research dentist and nurse, and trial personnel have undertaken any required GCP training.

The study will be supervised by a PMG. The co-chairs of this group will be Professors Clarkson and Ramsay and will consist of grant holders, representatives from the Trial Office and CTU. The PMG will meet at least monthly however in the setup stages this may be more frequent. In addition, the PMG will also meet at the annual Trial Steering Committee meeting.

The Trial Office will be based in the Dundee Dental School at the University of Dundee and will provide day to day support for the clinical centres and sites and through the Trial Manager and administrative positions who will provide a hub for dissemination of administrative and clinical support activities for the trial. At each of the clinical centres, the co-investigators will be responsible for clinical training and liaison with local practices.

The Trial Manager based in CHaRT (Aberdeen) will take responsibility for supporting the regulatory requirements (e.g. submitting any amendments to REC or local approvals) and the day to day transaction of feasibility study activities (e.g. central monitoring of recruitment activities or producing reports for the PMG).The Trial Manager, Trial Administrator and Trial Administrative Assistant at the Trial Office Dundee will take responsibility for the day to day

collecting, collating, handling and entering data., These activities will be supported by the CHaRT Clinical Trials Unit at University of Aberdeen.

The programmer at CHaRT will create, maintain and update all applications programmes for the feasibility study. These trial staff will be supported by CHaRT senior team: the CHaRT director, the Senior IT manager who will oversee all IT aspects of the study, while the Senior Trials Manager will provide mentoring and guidance to the trial manager and advice to the team on generic coordination issues. The Quality Assurance Manager will be responsible for advising on assessments of quality the trial, appropriate training of standard operating procedures, and will assist with any external monitoring and auditing of the trial.

12 ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be conducted in accordance with the principles of GCP.
In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the feasibility study.

A Research Ethics Committee (REC) favourable opinion, HRA (Health Research Authority) approval and NHS R&D approvals will be sought. The feasibility study will be conducted according to the principles of GCP provided by Research Governance Guidelines. A final report for the feasibility study will be submitted to the funder, Sponsor and the relevant REC within the timelines defined in the regulations.

The feasibility study will run under the auspices of the Trial office in Dundee Dental School & Hospital and CHaRT in the University of Aberdeen. CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. Both institutions are committed to the highest standards of research governance and seek to conform to all relevant governance guidelines and codes of practice as detailed in the Research Governance Framework and ICH guidelines for GCP. As well as ensuring that research is conducted according to the requirements set out in these documents, all research will be conducted with the written agreement of the relevant Multi-Centre and/or the Research Ethics Committee(s), and/or other relevant ethics committee(s) before starting recruitment. The CI will ensure, through the TSC and Sponsor that, adequate systems are in place for monitoring the quality of the trial and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial.

A study information leaflet will be given to each potential participant to inform them of the anticipated risks and benefits of taking part in the study. In particular, the trade-offs between possible short-term benefits and long-term risks will be explained. Informed signed consent forms will be obtained from the participants in all practices, by an individual who is trained in GCP. Patients will be given sufficient time to accept or decline involvement and are free to withdraw from the study at any time.

12.1 Research Ethics Committee (REC) review & reports

Research Ethics Committee (REC) approval, HRA (Health Research Authority) approval and R&D approvals for the trial will be sought before the study commences.

The main benefit of participating in this feasibility study is an altruistic one to improve care for patients with dental pain caused by inflammation of the pulp that would currently be treated with complex, expensive RCTx or extraction. A potential risk is that FP may delay the need for RCTx resulting in lengthier duration of symptoms and dental treatment, but all failures would be expedited for remedy. Conversely if the intervention is successful, we will have enabled 40 participants to avoid RCTx or extraction. The knowledge that one is superior in terms of clinical or cost effectiveness would be of benefit to patients, the NHS and society.

12.1.1 Ethical issues

The main ethical issue in the feasibility phase is the need to recruit participants to undertake an intervention (FP) which may not be fully in line with the participant's perceived values or preferences. Prior to obtaining consent it is essential that participants are fully informed about the process and outcomes (benefits as well as risks) of FP, the lack of comparative studies, and it is important that this information is presented in a balanced and comprehensible manner.

12.1.2 Annual reporting

Not applicable to feasibility study.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12.2 Peer review

The feasibility study protocol will be reviewed by the Trial Steering Committee on behalf of the funder (National Institute for Health Research Health Technology Assessment Programme) and by the Research Ethics Committee. The justification for the feasibility study and the proposed feasibility study design have been peer reviewed by independent expert panels as part of the application process to the funder. This involved 2 rounds of review as well as post award revision.

12.3 Public and Patient Involvement

During the feasibility study, patient and public perspectives will be included in several ways. The PPI planning, training and facilitation in the study will be guided by a dedicated PPI lead who works closely with public partners in the Health Services Research Unit (HSRU) public involvement group. The PPI lead will support the PPI partner on the project management group to review and discuss patient facing materials, recruitment processes and other aspects of the study conduct and dissemination. A patient advisory group will be established (facilitated by the PPI lead) and will meet during the feasibility phase to give patient perspectives which can be incorporated in the main trial development. Additional PPI input will be provided by two PPI partners on the independent steering committee. The PPI lead and the HSRU public involvement group will support researchers and PPI partners throughout the trial to ensure meaningful and accessible involvement.

12.4 Regulatory Compliance

The protocol and trial conduct will comply with the UK policy framework for Health and Social Care research (v3.3 07/11/17) and any relevant amendments.

12.5 Protocol compliance

Protocol non-compliances are departures from the approved protocol.

- prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

12.6 Notification of Serious Breaches to GCP and/or the protocol

If a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately.

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

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

12.7 Data protection and patient confidentiality

The Co-CIs and trial staff will comply with all applicable dental/medical confidentiality and data protection principles and laws about the collection, storage, processing and disclosure of personal data. The Co-CIs and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. Patients will be reassured that the data collected during the research is kept strictly confidential. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via usernames and passwords.
Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The Co-CIs and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by

those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the Co-CIs and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

All Co-applicants and oversight committee members (TSC and DMEC) will be asked to sign a competing interests form to confirm there are no conflicts of interest.

12.9 Indemnity

The University of Dundee is sponsoring the trial.

Insurance

The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the trial.

Where the trial involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity

The Sponsor does not provide trial participants with indemnity in relation to participation in the trial but has insurance for legal liability as described above.

12.10 Amendments

Approval for any amendment will be requested of the Sponsor who is required to categorise as substantial or non-substantial. No amendment will be made without the appropriate approvals. In the event that the CI needs to deviate from the protocol, the nature of and reasons for the deviation will be documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

12.11 Post trial care

The feasibility study will be conducted in accordance to the Declaration of Helsinki.

The Declaration of Helsinki states that "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be

disclosed to participants during the informed consent process" and that "in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions."
The protocol should describe any interventions, benefits, or other care that the sponsor will continue to provide to participants after the trial is completed and provide justification if continued access to the trial treatment(s) will not be funded. See the link for guidance
https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

12.12 Access to the final trial dataset

The trial statistician will have access to the final trial dataset and prepare reports for the Project Management Group, Trial Steering Committees and Data Monitoring and Ethics Committees. Trial investigator requests for access to the trial dataset will be considered by the Trial Steering Committee.

13 DISSEMINATION POLICY

13.1 Dissemination policy

On completion of the feasibility study, if it has been determined that progression to the main trial is not possible, the feasibility study data will be analysed and tabulated, and a clinical trial report will be prepared.

On completion of the feasibility study, if it has been determined that progression to the main trial is possible, the data from the feasibility study will be analysed and tabulated, and a clinical trial report will be prepared in conjunction with the clinical report of the main trial.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG. Once the main trial findings have been published, a lay summary of the findings will be sent to all involved in the trial. A trial publication/authorship policy will be agreed at the first TSC meeting.

13.2 Dissemination and outputs

If it has been determined that progression to the main trial is not possible, the findings of the feasibility study will be published in a peer reviewed journal.

This feasibility study investigates a treatment option identified as being potentially able to generate a significant cost saving for the NHS. We have found it to be of high interest to practitioners and patients. We will produce new knowledge which will be valuable for these and other key stakeholder groups both in the UK and internationally. We will use varied communication strategies to ensure that all stakeholder groups are updated throughout the feasibility study and aware of the feasibility study outcome.

Patients
We will work alongside our Patient Advisory Group and other PPI partners to ensure key individuals and organisations are appropriately targeted and will co-create strategies to actively engage patients and the public. Contemporary social media platforms in addition to other communication channels will be explored and used as appropriate at different stages of the trial.

NHS
The results of the feasibility study will be communicated directly to all participating dental practices. Members of the team may speak about the feasibility study at national conferences for GDPs such as the British Dental Association conference, meetings and conferences of the Faculty of General Dental Practitioners and local practitioner meetings. Our experience of conducting the feasibility study will be used alongside our successful approach of including participating practitioners to speak at meetings, giving them an opportunity to raise awareness of the rewards of research participation as well as increasing visibility of the main trial. We will produce clinical summary papers for clinician targeted journals.

Academic Community
Outputs will begin shortly after the feasibility study starts with publication of the study protocol and continue throughout the duration of the trial with publications targeting high impact journals and major conferences to present the ongoing work conducted in the trial.

End of Trial Dissemination Events
Final dissemination events will be organised to report on the decision to proceed to full trial after the feasibility trial end. This will include key stakeholders (e.g.- patients/national patient advocates, clinicians, NHS England-commissioners, GDP providers participating practices/participants) to deliver impact across wide audience.

The PIP feasibility study will be an exemplar of how research evidence can enter a data ecosystem to reduce waste in research by decreasing the time taken from publication to translation into practice. Ensuring timely publication, updating relevant Cochrane reviews and liaising with guideline development groups and early conversations with policy makers in service and education will facilitate change to improve the adoption of the research findings. During the PIP feasibility study information will be gathered about possible barriers and facilitators to implementation both from the patient and dental practice perspective. These will be communicated and discussed with groups responsible for policy change, education and guidance development during the trial period.

Members of the research team and PIP Steering Committee will disseminate research findings to the UK Chief Dental Officers, UK Health Departments and commissioners in NHS, Public Health England, NICE, SIGN and SDCEP. We will communicate directly with the British Dental Association, Faculty of General Dental Practitioners (FGDP), postgraduate deans and Royal Colleges.

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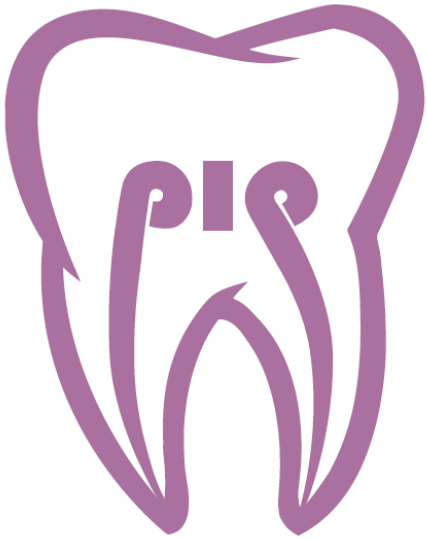
NHS
Health Research Authority



PIP Study Protocol

Pulpotomy or root canal treatment for the management of Irreversible Pulpitis in mature teeth

Version 2 16 May 2023

GENERAL INFORMATION

PROTOCOL VERSION 1.1 (09.05.2023)

IRAS NUMBER: 323138

ISRCTN:

SPONSOR: UNIVERSITY OF DUNDEE

TITLE PAGE

FULL/LONG TITLE OF THE TRIAL
Pulpotomy or root canal treatment for the management of **I**rreversible **P**ulpitis in mature teeth

SHORT TRIAL TITLE / ACRONYM
Pulpotomy for **I**rreversible **P**ulpitis (PIP Study)

PROTOCOL VERSION NUMBER AND DATE

Version History	Description of change
Version 1.0	REC Submission
Version 1.1	Updated for REC

RESEARCH REFERENCE NUMBERS

IRAS Number:	323138
ISRCTN Number:	TBC
SPONSOR Number:	2-054-22
FUNDER Number:	NIHR 129230

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator:
Signature: Date:

..../...../.....
Name: (please print):

.....

(Optional)

Statistician:
Signature: Date:

..../...../.....
Name: (please print):

.....
Position:

.....

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Sponsor	University of Dundee
Funder(s)	This study is funded by the National Institute for Health and care Research (NIHR) Health Technology, Assessment (HTA) Programme (project reference 129230). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
FP	Full Pulpotomy
GCP	Good Clinical Practice
GDP	General Dental Practitioner
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIL	Participant Information Leaflet
QA	Quality Assurance
QC	Quality Control
RCTx	Root Canal Treatment
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	**P**ulpotomy or root canal treatment for the management of **I**rreversible **P**ulpitis in mature teeth (PIP Study)	
Trial Acronym	PIP Study	
Trial Design	The **PIP Study** is a primary dental care, pragmatic, multi-centre randomised clinical trial, with an internal pilot phase, to compare Full Pulpotomy (FP) versus Root Canal Treatment (RCTx) in pre/molar teeth with symptoms indicative of irreversible pulpitis. The internal pilot phase will monitor recruitment and assess willingness of patients to participate.	
Trial Participants	Adult patients (16 years and older) seeking healthcare at NHS primary care dental practices with symptoms indicative of irreversible pulpitis.	
Planned Sample Size	Study: 50 Primary Care Dental Practices recruiting up to 530 participants.	
Treatment	**Full Pulpotomy (FP)** Removal of the inflamed coronal pulp keeping the radicular pulp vital **Root Canal Treatment (RCTx)** Current UK practice (ESE standard)	
Follow up duration	1 year	
Primary	**Clinical**: Clinical success at 1 year (no re-intervention or symptoms of pulpitis or apical periodontitis). **Economic:** Incremental net benefit of FP versus RCTx over a modelled life-time horizon.	**Primary clinical outcome:** Determined from treatment data and a clinical examination.
Secondary	**Clinical**: Radiographic success (absence of radiolucency on the 1 year in participant's initial intervention in the recall periapical radiograph). **Patient-reported**: Patient oral health related quality of life and dental pain at 7 days and 1-year, dental anxiety, satisfaction with care/treatment, adverse events **Economic outcomes:** Use of dental care services; costs to the NHS; costs to patients; general population preferences; intervention uptake predictions; incremental net benefit (study follow-up); and incremental cost-per QALY gained (over study follow-up and modelled lifetime horizon).	Data will be collected from data linkage and mining of routine administrative clinical data, case report forms, radiographs that will be assessed by the research team, participant reported questionnaires and interviews.

iv. FUNDER

National Institute for Health Research HTA Programme	£1,996,749.96

v. TRIAL SPONSOR

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vi. ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee (TSC)
The membership of the TSC comprises independent members along with the Chief Investigator Janet Clarkson or a nominated delegate. Other PIP grant-holders and key members of the Trial Office team (e.g., the trial manager) may attend TSC meetings. This group will meet regularly and send reports to the sponsor. Lay members and patient representatives are included.

Data Monitoring (and ethics) Committee (DMEC)
An independent Data Monitoring Committee (DMC) will be convened. The Data Monitoring Committee members are impartial and not involved in the running of the study. The members will meet to agree the terms of reference during the early phase of the trial. They will meet to review data approximately annually, although this is at the discretion of the DMC. No interim analysis is planned.

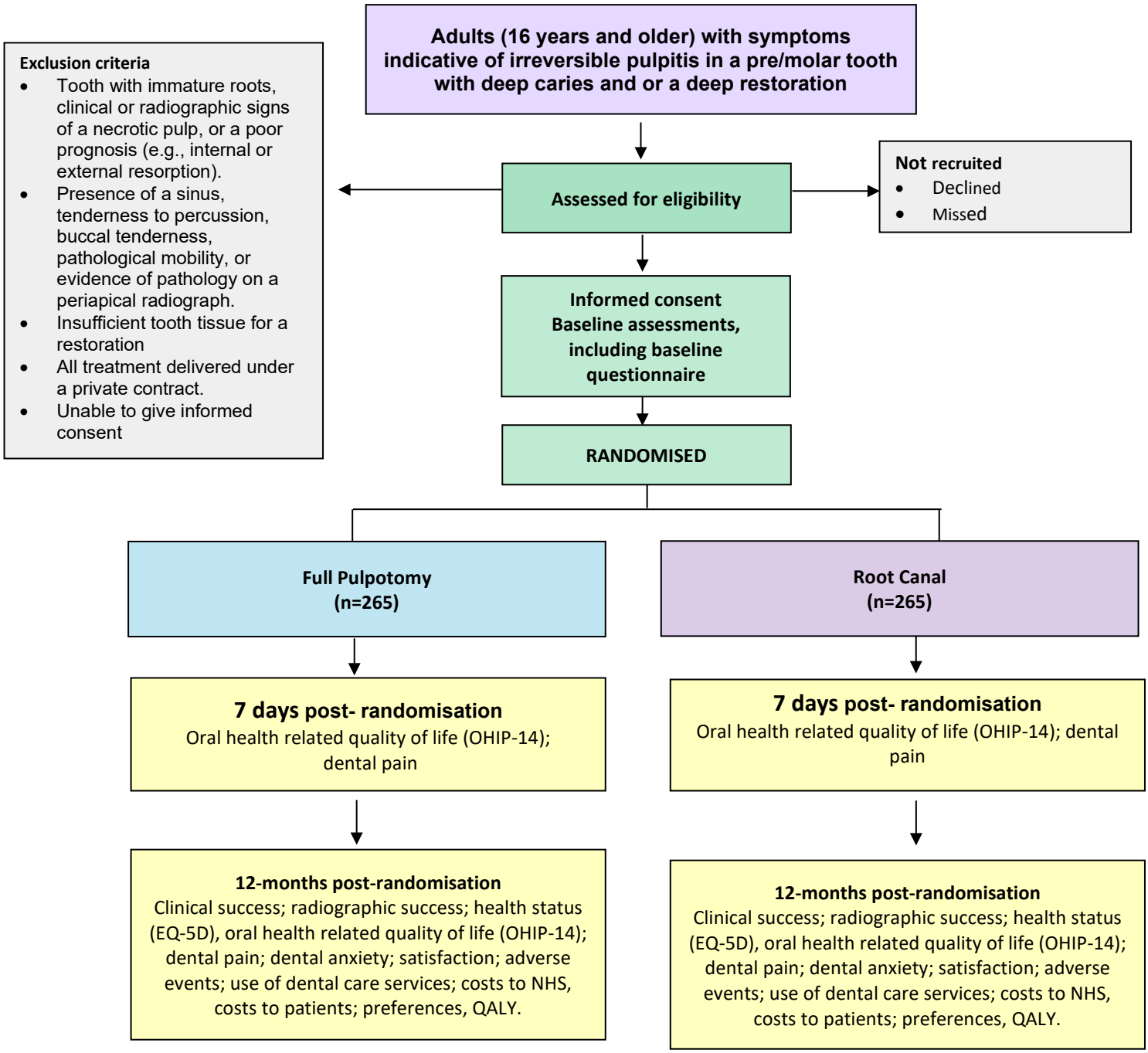
Trial Management Group (TMG)
The Trial Management Group meet regularly to ensure all practical details of the study are progressing and working well and everyone within the study understands them.

Operations Management Group (OMG)
The OMG will meet weekly in the early stages of the study to ensure smooth running of the study, troubleshooting issues as they arise, and ensuring consistency of action across the participating centres. A wider Project Management Group (PMG) will meet periodically to monitor the progress of the study.

vii. KEY WORDS:

Full Pulpotomy
Mature Teeth
Root Canal Treatment
Irreversible Pulpitis
Randomised Controlled Trial
Dental Primary Care
Severe Tooth Decay
Permanent Teeth

viii. FLOW DIAGRAM



1 BACKGROUND

The economic burden of dental disease is substantial, accounting for a global expenditure of $544.41bn annually(1). NHS expenditure on dental care in England exceeds £3bn per year and £527 million in Scotland, with over one million patient contacts every week (2). Most of this is due to dental caries, one of the most prevalent non-communicable diseases worldwide (3–6). The consequences are cumulative (7,8) and can negatively impact on quality of life and productivity.

1.1 What is the problem being addressed?

Dental caries result in localised and progressive demineralisation of the dental hard tissue; if undisturbed the bacterial insult will cause the pulp of the tooth to become inflamed. Persistent inflammation can lead to *irreversible pulpitis* (when the vital inflamed pulp is incapable of healing) (9), *pulp necrosis* and *abscess* formation.

Preserving the pulp in a healthy state with sustained vitality, preventing apical periodontitis (abscess) and developing minimally invasive biologically based therapies are key themes within contemporary clinical practice. The position statement from the European Society of Endodontology (ESE) (10) explains the challenge of managing deep caries and pulp exposure. PIP will investigate outcomes for partial irreversible pulpitis as this is the initial stage of the irreversible damage, confined to the coronal (crown) pulp whilst the radicular (root) pulp remains vital i.e., a healthy blood supply is maintained to the pulp tissue in the roots of the tooth. Removal of the coronal pulp with a ***Full Pulpotomy*** (FP) may keep the radicular pulp vital and thereby avoid the need for complex ***Root Canal Treatment*** (RCTx) or extraction. We will adopt FP as the new technology and recommended by ESE (10) for general practices because a partial Pulpotomy is difficult without magnification (specialist equipment).

2 RATIONALE

Most adults experience decay and the 2009 Adult Dental Health Survey reported that 85% have at least one restoration. Management of dental caries centres around primary prevention and/or operative intervention involving caries removal prior to the irreversible pulpitis stage. If this fails, RCTx involving complete removal of the pulp is the only option currently offered in primary dental care (other than extraction) but it is a technically demanding procedure, especially in premolar and molar teeth, and increases patient anxiety (11). It is also time consuming and costly to the NHS and patients. In Scotland, 111,000 RCTxs were provided in 2017/18 costing £8.9m. Approximately 80% of this cost relates to RCTxs on premolar and molar teeth. Extrapolating these figures to England suggests the total cost of this treatment may be in excess of £71m per year.

The PIP study team engaged with patients from a Primary Care Dental practice, patient representatives and the public who highlighted the need to develop more modern dental techniques which aim to preserve rather than remove tooth tissue. This research is important to establish whether FP will, in addition to relieving pain, provide a treatment that is more acceptable for patients, avoiding a complex treatment with multiple lengthy visits, possible crowning and a tooth that, if RCTx fails, is frequently extracted and a further fixed or removable prosthetic replacement needed. Therefore, in addition to cost savings, FP may improve patient quality of life through better oral health, fewer episodes of dental pain and possible reduction in dental anxiety.

The recently published commissioning standard in NHS England Restorative Dentistry defined the complexity of clinical and technical procedures according to levels of care 1, 2 and 3 (with increasing complexity). They also reflected the competency of clinicians and the equipment required to deliver care of that level of complexity (12). Complex RCTxs are considered level 2 and 3 and should be referred to specialists or dentists with special interest. The new FP technology could make management of complex cases possible in primary care by Primary Care Dental practitioners (GDPs), avoiding the need for extraction or the increase in cost and burden on patients in referral.

Feasibility Study
As FP is a novel technology for NHS primary dental care, we completed a feasibility study to determine whether it is possible to carry out the FP procedure within dental primary care. The feasibility study looked at the practicalities of providing the FP procedure in dental primary care, assessed the training needs of dentists, developed a training package and recorded patient satisfaction and pain after treatment. The feasibility study found that the FP treatment could be delivered in a Primary Care Dental Practice setting. Patient satisfaction recorded at 7-days post treatment showed that in the majority of cases, patients were satisfied with the treatment after 7 days, however some patients reported mild pain after the procedure which is to be expected.

2.1 Why this research is needed now
The importance of this topic to GDPs is clear from the responses to a survey hosted on the Scottish Dental Practice Based Research Network (SDPBRN) website, completed by 168 dentists from across the UK. It indicated that GDPs were very interested in the health technology to be tested in PIP, but that clinical training would be required for FP. Around 91% of responding dentists did not offer Pulpotomy to NHS adult patients and many cited contract restrictions and the costs of bio-ceramic materials as barriers. Overcoming these issues for PIP had already been discussed with UK Chief Dental Officers. Whilst the majority of dentists (97%) offered RCTx for uncomplicated teeth this reduced to 68% and 20% for teeth with a moderate or complex risk of adverse outcomes indicating case selection will be required in PIP. Respondents confirmed our preliminary finding from analysis of tooth-specific data from NHS Scotland national datasets that around 15% of root treated teeth required re-intervention with repeat RCTx, surgical endodontics or extraction at 1 year.

Systematic reviews and randomised controlled trials suggest that Pulpotomy may offer comparable treatment success rates and might be a cost-effective alternative to RCTx, but the evidence base is weak and sparse for the management of vital mature teeth with clinical signs of irreversible pulpitis in the UK NHS (13–16). Two randomised controlled trials conducted in an adult population reported a success rate of Pulpotomy comparable to RCTx (97.6% v 98.3% at 1 year) (17); 85% v 87.5% at 18 months (18). However, both trials were conducted outside of the UK and in the secondary care setting. These studies have limited generalisability due to lack of methodological rigor, difference in the health systems and the clinical approaches used. There is an ongoing trial in the UK (19) looking at this research question in a secondary care setting. The Chief Investigators of the ongoing study are co-applicants in PIP.

RCTx success rates vary considerably in the literature. A systematic review (20) together with recent studies conducted internationally (21–23), including primary and secondary care,

concluded that the 2- to 10-year survival outcomes of RCTx ranged from 72% to 94.4%. Treatment success rates in primary care dentistry in Sweden, according to periapical status, was 62% immediately after treatment (24); however, a review on RCTx survival in Primary Care Dental Services in England and Wales estimated 74% of root canal treated teeth pass through 10 years without re-treatment, apical surgery or extraction and the survival rate was above 90% in the first year (22). Evidence from a systematic review and a retrospective follow-up study suggests that the success rate of Pulpotomy for permanent posterior teeth may be over 90% at one-year follow-up, but the participants in the included studies were not representative of UK NHS practice (13,25).

Our Patient and Public Involvement (PPI) work has included interviews with patients attending for dental treatment and discussion at a patient forum. It found that patients would value alternative treatment to avoid RCTx, be willing to undergo a FP, be randomised to that or RCTx and outcomes important to them have been included.

2.2 COVID-19

The COVID-19 pandemic had a significant impact on the provision of dental care. Primary care settings were forced to close in March 2020 as part of the UK nationwide “lockdown”, which impacted on and caused a backlog in patient care, and the effects of this are still being seen today. These are challenging times for dentists. There is a heightened demand for dental care due to the backlog as a result of restricted access to treatment and the impact of this will be felt for some time.

Our learning from the COVID-19 pandemic strengthens the argument for conducting this study and reinforces the need for the evidence base to be established. RCTx is commonly completed over a number of visits and is a technically challenging procedure. FP treatment is usually completed in a single visit. This means FP could have a positive impact in reducing the number and duration of patient contacts within a dental practice.

3 AIM, OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim : To assess the effectiveness and cost-effectiveness of FP as compared to RCTx for adults with mature pre/molar teeth with symptoms indicative of irreversible pulpitis.

3.1 Primary objectives

- To compare the clinical success of FP with RCTx (no re-intervention or symptoms of pulpitis or apical periodontitis) at 1 year.
- To compare the costs and benefits of FP with RCTx over a modelled life-time horizon.

3.2 Secondary objectives

- To evaluate radiographic success (absence of radiolucency in participant’s initial intervention), patient health related quality of life, dental pain, dental anxiety, satisfaction with care/treatment and adverse events at 1 year. Patient health related quality of life and dental pain at 7 days.
- To determine general population preferences for treatment and outcomes and predict uptake, NHS and patient perspective costs; incremental net benefit over the study follow

up; and incremental cost per QALY over the 1-year follow-up and extrapolated over a modelled lifetime horizon.
- To explore the implementation of technologies and the mechanisms of impact including acceptability of interventions to patients and clinicians.

4 TRIAL DESIGN

The PIP Study is a pragmatic, primary dental care, multi-centre, two-arm patient randomised control trial with an internal pilot comparing the clinical and cost effectiveness of FP compared to RCTx in pre/molar teeth of adults (16 years and older) showing signs indicative of irreversible pulpitis. PIP has been designed as a non-inferiority trial for the primary clinical outcome.

4.1 Health Technology being assessed

Health Technologies:

Full Pulpotomy (FP) will be compared to Root Canal Treatment (RCTx)

Full Pulpotomy:

- Pre-operative peri-apical radiograph
- Access cavity preparation
- Where caries removal is necessary, this should be complete and carried out in a systematic way removing it completely at the periphery of the cavity then progressively over the pulp, for controlled reduction in the bacterial load preventing further bacterial contamination of the pulp
- Once the pulp has been reached a new sterile bur should be used with water coolant to remove pulp to the level of the radicular/root canal orifices.
- Haemostasis (within 5 minutes) and disinfection should be achieved with cotton pellets soaked with minimum 2% sodium hypochlorite under dental dam isolation. Do not use bleach.
- If haemostasis cannot be achieved after 5 minutes the tooth should undergo RCTx (pulpectomy) as per the clinician's normal practice
- Once haemostasis has been achieved for all root canals (all root canals have to be vital i.e., bleeding stopped), a hydraulic calcium silicate cement should be place directly onto the pulp tissue
- Immediate post-operative radiograph to be taken.

Root Canal Treatment:

Dentists should carry out RCTx according to current practice (i.e., usual cleaning and irrigation technique, materials and obturation) and established standards (e.g., dental dam, post-operative radiograph).

4.2 Clinical Training

Preparatory work confirmed the need for and importance of effective clinical training for the FP technique. The clinical training will be delivered over two sessions. The first session will be delivered remotely and include the background of and evidence for FP, along with theoretical training in the FP technique. The second session will be a hands-on training session at each clinical centre.

Participating dentists will already be trained in delivering RCTx in Primary Care Dental practice and will be familiar with the current guidelines. Training will therefore be a refresher of the ESE guidelines for RCTx and an opportunity for peer-review and understanding of best practice.

Dentists will be trained to deliver the FP as described in Section 4.1. As FP will be a new technology to most GDPs, instruction will demonstrate the procedure and establish the standard level of care. Instruction in access cavity preparation and choice of materials will include a hydraulic calcium silicate cement (e.g., Biodentine). 3D printed artificial teeth (Figure 1) are routinely used for RCTx training but their use in training in FP techniques and success assessment is novel. We estimate 4 teeth for each dentist will be sufficient for them to feel confident and competent in the technique, but further 3D teeth can be used as required and can also be used for any refresher training.

Formative assessment for the dentists will include self-assessment using a success checklist that measures success against the FP training criteria below. Success in training will be determined using the FP training criteria below to evaluate the FP procedures carried out on the 3D teeth and assessment of post-operative radiographs taken of the 3D teeth. Ultimately the decision as to whether a dentist has been successfully trained in the FP technique is a clinical judgement made by the study's clinical team.

FP Training criteria:

- Access cavity preparation (complete removal of the pulp chamber roof).
- Adaption of the Biodentine material (covers the floor or pulp stumps, adequate thickness of 2mm, no porosity)
- Adequate final seal (no excess Biodentine on walls preventing peripheral seal).

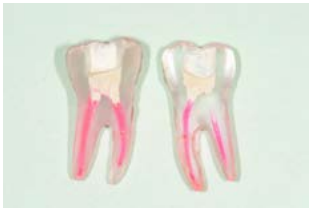


Figure 1 – Example of sectioned Endo reality 3D tooth used for training showing FP procedure.

Participating dentists will already be trained in delivering RCTx in Primary Care Dental practice and will be familiar with the current guidelines. Training will therefore be a refresher of the ESE guidelines for RCTx and an opportunity for peer-review and understanding of best practice.

4.3 Study Process and GCP Training

In addition to the clinical training, Study Process and GCP training will be provided for anyone involved in the study at the site. This will:

- Introduce the study design and give an overview of the protocol
- Present practical guidance on study processes including consent, randomisation, data collection and study paperwork.
- Introduce the study database to members of the team who will have access.
- Provide training in Good Clinical Practice as necessary.

4.4. Population

We will recruit 530 adults (16 years and over) seeking healthcare at NHS Primary Care Dental practices with symptoms indicative of irreversible pulpitis [as defined by ESE (10)] in a pre/molar tooth with deep caries and/or a deep restoration.

4.5 Patient Participant process

Patients will contact their dental practice when suffering from toothache and in pain. There are many causes of pain, but through a triage process, possible cases of irreversible pulpitis can be flagged to the study dentist prior to the patient's appointment.

Local procedures at the participating dental practices are different and the timing and mode of approach may vary to accommodate the specific circumstances at each site.

The patient will be given an information pack which includes the Participant Information Leaflet and an invitation letter. The patient will have time to digest this information and ask any questions they may have. The dentist will make sure the patient has time to adequately consider whether they would like to take part before starting any treatment.
If the dentist thinks the patient may be eligible, they will explain the study to the patient. To confirm eligibility, a periapical radiograph will be taken prior to any treatment.
If a patient agrees to take part, they will be asked to complete a consent form. Once the consent form is signed, the recruited participant will be allocated a study ID number, generated by the study database online, that will be used on all study documentation. The participant will also complete a baseline questionnaire.

Each recruited participant will then be randomised to either receive a FP or RCTx . Depending on the time available, treatment may be at the same appointment or will be booked in for a time in the future. Once treatment commences, regardless of the treatment arm a patient is allocated to receive, if the dentist considers that another treatment is more appropriate, they should proceed as clinically appropriate and document this on the treatment CRF. Should a recruited participant change their mind and not want the treatment allocated, the dentist will follow the course of treatment the participant requests and again this will be documented on the CRF.

Following their treatment, participants will be given a 'What's Next' document. This will outline the next steps for their time in the study (12 months) and will also include a £15 voucher to thank them for taking part.

Both the pre-operative and post-operative radiographs will be uploaded to the study database along with CRFs and associated paperwork.

Participants will be contacted by their preferred method (email or phone call) by the Study Office at least 7 days post randomisation to complete their 7-day questionnaire. One reminder will be issued if no response. No further attempts will be made after 14 days.

All participants can choose if they are willing to take part in a qualitative interview. If interested, participants will consent to a qualitative interview by indicating this on an optional statement on the study consent form. The details of how this will be arranged are included in the 'What's Next' information and outline of the next steps. A member of the process evaluation team will contact a sample of participants who have consented to a qualitative interview, approximately four weeks after randomisation.

After the initial intervention, participants will receive any treatment deemed clinically appropriate by their dentist as per normal practice.

A follow-up assessment for the study will take place at 12 months. Participants will be invited for a clinical final assessment with their dentist. Periapical radiographs will be taken and uploaded to the database by the study dentist.

In advance of the anniversary of their treatment date, participants will receive a final questionnaire via their preferred method (post, email). For those opting for postal questionnaires, these can be returned directly to the Study Office (a freepost return envelope will be included), or they can be returned to the dental practice when the participant attends their final assessment appointment. First reminders will be emailed, posted, or texted to participants (according to their stated preference). A second reminder (by telephone) will be attempted but if there is no response by telephone, a final postal reminder will be sent.

At the final assessment appointment, participants will receive a second £15 voucher and a thank you letter for taking part in the study.

5 TRIAL SETTING

This is a multi-centre study set in primary dental care. Dentists (GDPs) will be recruited from fifty primary Care Dental practices from UK regions with established research networks and experience of collaboration (Scotland and England). All GDPs approached and expressing interest will be asked to complete a Site Initiation Questionnaire (SIQ) for their dental practice.

6 PARTICIPANT ELIGIBILITY CRITERIA

The eligibility of all participants will be assessed and determined by their dentist following clinical and radiographic examination.

6.1 Inclusion criteria

- Adults (16 years and older) with symptoms indicative of irreversible pulpitis [as defined by ESE (10)] in a pre/molar tooth with deep caries and or a deep restoration.

6.2 Exclusion criteria

- Tooth with immature roots, clinical or radiographic signs of a necrotic pulp, or a poor prognosis (e.g., internal or external resorption).
- Presence of a sinus, tenderness to percussion, buccal tenderness, pathological mobility, or evidence of pathology on a periapical radiograph.
- Insufficient tooth tissue for a restoration
- All treatment delivered under a private contract.
- Unable to give informed consent

7 TRIAL PROCEDURES

The PIP Study team have considerable experience of recruiting to NIHR HTA trials in dental primary care and lessons learned will be applied to ensure optimal recruitment and retention.

7.1 Recruitment

7.1.1 Recruitment of practices

Primary Care Dental Practice is the main provider of NHS dental care in the UK. We aim to recruit 50 GDPs with some research experience from across the UK via our partner research networks and dentists who may or may not be active in other dental trials. One or more dentists will be recruited at each practice to maximise recruitment at each site. A list of participating practices will be kept up to date and provided on the public study website: https://w3.abdn.ac.uk/hsru/pip.

PIP has benefited from recruitment efficiencies from conducting a Feasibility Study. In addition, the CI from the University of Dundee has strong links with the deputy CI from the Clinical Trials Unit at the University of Aberdeen. Together they have well established networks formed as a result of successfully undertaking multiple large scale NIHR HTA studies in Primary Care Dental Practice. Recruitment will be open to all NHS Primary Care Dental Practices in the participating regions. Practices that have successfully recruited to and delivered previous dental HTA studies will be targeted through our partner research networks.

Following an expression of interest, an appraisal of each practice's ability to recruit participants will be conducted, including evidence of a sufficient supply of eligible patients from their routine patient base or new patient population. This will include confirmation of providing RCTx for pre/molar teeth from practice management systems or routine data. Digital X-ray facilities at the practice will be preferred but are not essential.

7.1.2 Recruitment of participants

Study dentists will identify patients presenting at their clinic/practice with symptoms indicative of irreversible pulpitis who meet the inclusion criteria and explain the study. Patients with these symptoms who contact the practice will be informed the study is taking place at their practice. Potentially eligible patients who express interest will be given a Participant Information Leaflet (PIL) and an appointment will be arranged for their treatment as per current clinical practice. If a patient presents at an appointment requiring immediate treatment, sufficient time to make an informed decision regarding willingness to participate will be given. At the treatment visit the

patient will be given the opportunity to clarify any questions prior to consent being obtained. In some cases, treatment could be on the day the patient attends the practice.

7.1.3 Screening
The eligibility of all participants will be assessed and determined by their dental practitioner following clinical and radiographic examination. Our learning from the Feasibility Study shows that practice staff undertaking telephone triage may be able to flag up patients who may be eligible to take part and guidance will be provided for practice team members who may find this useful. If more than one tooth is eligible, a study tooth will be selected at random. A paper screening log will be kept at site, to assist with the triage process as required.

7.1.4 Thank you vouchers
Participants will receive £30 in Love2Shop vouchers as a thank you for participating in the study – £15 following consent and £15 at the end of follow-up at 12 months. Vouchers will be accompanied by a 'What's next' document at the start of the study, and a thank you letter at the final follow up. They will be given to the participant by a member of the dental team or posted to their home address by the study team if required.

7.2 Consent
Informed consent to participate in PIP will be sought and obtained according to the principles of Good Clinical Practice (GCP) . When attending an emergency or routine visit at their dental practice, potentially eligible participants will be given a PIL detailing the study process, including the risks and benefits of FP and RCTx. Informed signed consent will be sought either at that visit or a subsequent treatment visit after sufficient time for the potential participant to accept or decline involvement and will be obtained using a standardised consent form by the participant's clinician who will be appropriately trained. The participating clinicians will verbally reiterate the information contained in the information leaflet and answer any questions that patients may have about the study as part of the informed consent process. Participants will be asked to consent to: participation; follow up; contact to invite them to take part in a qualitative interview about their experience in the study(optional); contact in the future about this and other relevant research; electronic tracing using NHS data (and if relevant BUPA data); and data linkage with routine NHS data sources (such as NHS BSA, Public Health Scotland).

It will be explained that entry into the study is entirely voluntary, and that treatment and care will not be affected by their decision, and they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected to date of withdrawal cannot be erased and will be used in the final analyses.

Participants who cannot give informed consent (e.g., due to impaired cognition) will not be eligible for participation. Following informed consent, if a participant loses capacity, they will be withdrawn from the study.

Patients who are not able to read or write (but who have capacity and who can speak English sufficiently to understand the information being provided orally) can agree to take part in the study. In such cases, the study team will provide them with written literature about the study

and read and discuss this information with the potential participant. There should also be a discussion about the support networks to which the patient has access to facilitate their participation in the study (e.g., help to complete questionnaires). If the potential participant is fully informed and wishes to take part in the study, they will be asked to sign or make their mark on the consent form. Their agreement to take part in the study should be witnessed by someone independent from the research team.

Procedures to seek and gain informed consent from eligible potential participants are to be agreed and confirmed by Research Ethics Committees with responsibility for reviewing applications for research. The application for approval is made via the NHS National Research Ethics Service.

7.2.1 Obtaining e-Consent

To cater for participant preference, participants may opt to consent using an e-consent form via the secure web-based study management system hosted by the Centre for Healthcare Randomised Trials (CHaRT). If this option is preferred, potentially eligible participants will be asked during screening to provide their email address which will be entered into the secure web-based study management system by the dental practice staff. Participants will be sent an email from the secure website with a link to verify their email address. When their email address is verified, participants will be automatically emailed the PIL and a link to the participant e-consent form for their unique study number. The e-consent form will be identical to the approved paper version of consent form, with the approved PIL version number and date automatically populated. The participant will be asked to provide their signature online via a signature box using a finger tracing via a touch screen or using a mouse. Should participants prefer to use e-consent this may be provided at any time prior to the treatment visit or on the day of treatment. Clinician countersignature will be recorded on the e-consent only after discussion has taken place with the participant about the study and any questions have been answered. Any e-consent obtained will be verbally confirmed by the site at the treatment visit. Participants will be emailed a copy of the e-consent form for their own records and a copy will be retained in the Investigator Site File and TMF.

The email address of potentially eligible participants who are sent the study information and decline to take part will be deleted from the trial management system after 3 months. The study management system used to record e-consent has a clear audit trail with tracking of all inserts or updates made, database interactions logged against a user and date/time and the audit trail can be downloaded and analysed at any time by authorised users.

7.3 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

A log will be maintained of patients who were approached about the study but declined to participate or found not to be eligible. Where available, a reason why the patient was not eligible or why they declined will be recorded. No identifiable details will be recorded other than year of birth.

7.3 Randomisation

Randomisation will be at patient level. Eligible and consenting patient participants will be randomised via the web-based application, both hosted by CHaRT.

The randomisation algorithm will use recruitment site, premolar/molar tooth and primary caries yes/no as minimisation covariates to allocate treatment intervention and control groups in a ratio of 1:1. A random element will be incorporated into the randomisation algorithm. The person with delegated authority will access the web-based system. Patient screening identification initials and recruiting site will be entered into the web-based system which will return the allocation status. At randomisation, an email will be sent to the site research team, including the PI, and the trial office, informing them of the allocation.

There is a manual back-up method for conducting randomisation should the situation arise where the website is completely unavailable. This is fully supported by the study office and also the CHaRT programming support team.

7.4 Blinding

Due to the nature of the interventions, blinding is not possible in this study

7.5 Emergency Unblinding

Not applicable.

7.6 Baseline data

At baseline socio-demographic characteristics of age, gender and eligibility for free dental treatment will be recorded. Prior to randomisation and treatment, baseline health related quality of life (EQ5D), oral health related quality of life (OHIP-14), pain, and related oral health behaviour will be collected via a participant self-reported questionnaire.

7.7 Outcome measures

7.7.1 Clinical Outcomes

Clinical outcomes and details of treatment will be recorded on the CRF at all visits. It will record whether the treatment was delivered as per randomisation, clinical and participant reported signs and symptoms, findings of any radiographs taken, the reason for and detail of dental treatment provided for study teeth. Routinely collected administrative treatment data may supplement.

- **Clinical success at 1-year post-randomisation**: No re-intervention (including extraction) or symptoms of pulpitis or apical periodontitis.
- **Radiographic success at 1-year post-randomisation**: Absence of apical radiolucency in the periapical radiograph in participant's initial intervention. All radiographs will be independently assessed by two clinical researcher using established criteria to judge success of treatment. Digital x-rays will be uploaded to the secure study management system and digital images of wet films made by the Study Office.

If a participant does not attend their 1-year assessment, they will be contacted for information remotely and routine data assessed if consent was obtained to do so.

7.7.2 Patient-reported Outcomes

These will be collected at 7 days post-randomisation and 1-year post-randomisation using the participant's preferred method (telephone, email, post, or in the dental practice). Baseline questionnaires will be completed prior to treatment and randomisation.

- **Dental pain** will be assessed at 7 days and 1 year using a 10-point Visual Analogue Scale (VAS), the most used validated pain assessment tool.
- **Oral Health Related Quality of Life** will be assessed at 7 days and 1 year using the Oral Health Impact Profile 14 (OHIP-14). OHIP-14 is the most commonly used validated oral health-related quality of life measure and has been used successfully in previous HTA trials.
- **Health status** will be assessed using the generic EQ5D at 7 days and 1 year, consisting of five dimensions of HRQoL.
- **Dental anxiety** will be assessed using the validated MDAS criteria at 1 year
- **Patient Satisfaction** will be assessed using the NHS England Commissioning of Dental Services Guidelines Patient Reported Experience Measures (PREMs) (26) at 1 year.

7.7.3 Health Economic Outcomes

The use of NHS primary care dental services will be collected at a tooth level, sourced from dental practice CRFs and routinely collected claims data (Public Health Scotland). Further resource use including secondary care will be obtained through routine data linkage e.g., NHS BSA, Public Health Scotland and from patient reported questionnaires.. Costs of the use of general NHS services for dental problems (e.g., A&E and GP practice attendance for pain), patient perspective costs (e.g., time off work, privately purchased care and over the counter medications for pain) and EQ-5D-5L data for QALY calculation will be sourced from participant questionnaires. Unit costs of time and travel will be estimated from external data available from the SCRIPT trial (17/127). A discrete choice experiment (DCE) with an online representative sample of the UK general population will be undertaken to elicit Willingness to Pay (WTP) for FP and RCTx, together with associated and patient relevant study outcomes (See Section 9.10.2) and to estimate uptake. Data to populate the life-time Markov model will be sourced from a combination of study results (costs, QALYs, treatment events), WTP from the DCEs, routine data, and systematic literature reviewing (See Section 9.10.4).

7.7.4 Clinical fidelity to study interventions:

Clinical fidelity of all study teeth will be independently assessed by two members of the study clinical team. The clinical team will provide dentists with a PIP treatment booklet outlining essential treatment criteria, e.g., absence of apical radiolucency pre-operatively, access cavity preparation, adaption of the Biodentine material and adequate final seal. The clinical team will also use the criteria to evaluate post-operative radiographs uploaded to the secure study database by the participating dentists. Ultimately the decision as to whether fidelity with the protocol has been maintained is a clinical judgement, made by the clinical team. If further action or training is required, this will be flagged up by the clinical team.

Fidelity assessment for FP

- Access cavity preparation (complete removal of the pulp chamber roof).
- Adaption of the Biodentine material (covers the floor or pulp stumps, adequate thickness of 2mm, no porosity)
- Adequate final seal (no excess Biodentine on walls preventing peripheral seal)

Fidelity assessment for RCTx

Clinical fidelity will be measured as per the Quality Guidelines Consensus report of the ESE 2006 (27):

- Access cavity preparation (complete removal of the pulp chamber roof)
- all root canals should be obturated to 0-2 mm from the apical terminus,
- root filling well adapted to the canal walls with minimal voids
- adequate final seal

7.7.5 ***Study Monitoring/reassurance***

Experienced co-design of PIP confirmed the benefit for dentists of monitoring and feedback. Examination of pre- and post-operative radiographs by the clinical research team will identify issues of case selection. This will provide the opportunity for confirmation of checklist and success criteria, identifying supplementary training needs and/or reassurance if required. Should feedback and further training be required, a member of the clinical research team will contact the dentist.

7.8 Process Evaluation

A mixed-method process evaluation will complement the outcome evaluation according to MRC guidance (28). It will investigate implementation (particularly any differences between dentists), mechanisms of impact (including acceptability to patients and dental teams) and context such as how dental contract and dental practice factors influence the delivery of the intervention. The process evaluation will allow identification of barriers and facilitators to implementation. Methods such as self-report questionnaires, analysis of key documents and interviews with patients and dental staff will be used (see Section 9.11).

7.9 Withdrawal criteria/ change of status

Participants remain in the study unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status, except for complete withdrawal of consent, means the participant will still be followed up for all study outcomes wherever possible. All data collected through the screening log up to the point of complete withdrawal may be retained and used in the analysis.

If participants wish to withdraw from the study they will be asked if they wish to withdraw from all study activity, from receiving treatment, completing questionnaires, or attending 12 month

follow up appointment. For participants who withdraw from active study follow-up, routine follow-up data from GDP records will be used for study purposes unless the participants explicitly withdraw permission.

Participants who lose capacity to consent during the study will remain part of the study unless a decision is made by family or carers for the participant to be withdrawn. In the case that a participant is withdrawn, any identifiable data already collected with consent would be retained and used in the study. No further data will be collected, or any other research procedures carried out on or in relation to the participant.

Participants who do not attend for follow-up assessment but for whom any outcome data are available will be included in an intention to treat analysis.

7.10 End of Study

The PIP Study end date is 30 June 2024.

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

7.11 Post-Study Care
Once the randomised course of treatment has been completed on the study tooth, participants are followed up as normal by their NHS GDP, for any study tooth or other dental requirements or issues. Study tooth specific issues are recorded up until the 12 month follow up has been completed, after which time the management of the study tooth reverts to purely NHS care as previously provided. For the duration of the study, all non-study tooth care is provided by the GDP as normal.

8 ADVERSE EVENTS

PIP involves two procedures, a Full Pulpotomy and a Root Canal Treatment. Root canal treatment is a well-established procedure in current NHS clinical practice. Whilst a Full Pulpotomy is a novel treatment in NHS primary care clinical practice, in terms of clinical procedure it is more conservative than the established Root Canal Treatment and could be considered as the same technique that is used in the initial stage of a Root Canal Treatment. We do not anticipate any safety concerns in PIP. The dentists taking part will be fully trained in both techniques and patients will receive the usual standard of care treatment from their dentist during and following the intervention as normal.

8.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect Or is otherwise considered serious by the treating clinician (PI)

Adverse events are **not**:

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

Only Adverse Events (AEs) and Serious Adverse Events (SAEs) that have a reasonable causal relationship to the Full Pulpotomy Treatment or Root Canal Treatment in the study tooth will be recorded.

8.2 Adverse Events

The following events are anticipated and are captured as primary or secondary outcomes rather than being captured through Adverse Event or Serious Adverse Event reporting processes and reflect the routine care the study is designed to measure:

- Further failure of tooth with associated signs or symptoms (e.g., pain, infection, swelling, periodontitis)
- Failure due to peri-radicular pathology with associated signs or symptoms (e.g., pain, infection, swelling, periodontitis)
- Dental infection associated with the study tooth
- Further treatment required (under local anaesthetic and/or general anaesthetic)
- Perforation
- Hypochlorite related injury
- Tissue trauma
- Loss of instrument
- Tooth cracking
- Crown fracture
- Root fracture
- Broken instrument in tooth
- Inability to complete Root Canal Treatment

8.3 Recording and reporting of SAEs

8.3.1 Detecting SAEs
SAEs will be recorded from the time a participant consents to join the study until the end of their follow up. Events that are serious but are not related to FP or RCTx in the study tooth will not be recorded as SAEs. Elective admissions and hospitalisations for treatment planned *prior to* study intervention, where appropriate, will not be considered as an SAE.

8.3.2 Recording SAEs
Once causality has been evaluated, SAEs will be captured on an SAE form. In addition, death for any cause (related or otherwise) is recorded on the SAE form.

8.3.3 Evaluating SAEs
Seriousness, causality and expectedness should be evaluated.

Assessment of Seriousness
The local investigator (PI) should assess seriousness as defined in Section 8.1.

Assessment of Causality
Each SAE should be clinically assessed for causality based on information available and reviewed as new information becomes available. i.e., relationship of SAE to the study intervention. All SAEs (other than those listed above as anticipated events and recorded elsewhere) judged as having a reasonable suspected causal relationship to the study intervention will be considered as SAEs. Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness
When assessing expectedness refer to the anticipated events listed in Section 8.2.

8.3.4 Reporting SAEs
Reporting responsibilities of the PI
It is the responsibility of the Principal Investigator (PI) dentist to check for AEs when participants attend for treatment / follow-up.

- Using medical judgement in assigning seriousness, causality and providing an opinion on whether the event was anticipated
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs are recorded and reported to the sponsor in line with the requirements of the protocol.

To report an SAE to the Study Office, the Investigator can either complete a hard copy of the SAE form and email it to the Study Office or complete the SAE form on the study website. If the SAE form is completed on the study website the Trial Manager will be automatically notified.

Reporting responsibilities of the CI
The Sponsor will delegate assessment of SAEs to the CI. If, in the opinion of the PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the Sponsor within 24 hours of receiving the signed SAE notification. If the CI judges an event to be Serious, Related and Unexpected then she will report it accordingly. The Sponsor cannot downgrade an assessment from the PI or CI. If the CI wishes to downgrade an assessment from the PI, the PI's agreement to the revised assessment must be obtained and the discussion documented. Any disparity will be resolved by further discussion between these parties – the discussion will be documented.

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

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size

Given the wide range of values available in the literature regarding RCTx's success rate varying from 62% (24) to 98% (17), we assumed a proportion of successful RCTxs of 0.85 (P1). This value was supported by our survey, where dentists estimated the failure rate of RCTxs at around 15%, and by Scottish routine data. There is evidence from randomised controlled trials to suggest that the proportion of successful pulpotomies is comparable to the proportion of successful RCTxs at 1 year, but slightly lower (15, 17-18) therefore we assumed a proportion of successful pulpotomies of 0.84 (P2). Our survey suggested that dentists consider that FP could be regarded as non-inferior to RCTx as the benefits in patient and economic outcomes are hypothesised to be superior for FP. The survey dentists deemed that the margin of non-inferiority acceptable is 0.12 so that P2-P1>-0.12. The sample size was estimated using Blackwelder's formula (29). A trial of 372 participants (186 per arm) is required for the lower bound of the 95% confidence interval to exclude -12% with 90% power. Allowing for 30% drop-out, we aim to recruit 530 participants. Our patient reported primary outcome will be OHIP-14 at 1 year. We aim to detect a mean difference of 2.7 points in the OHIP-14, deemed to be clinically meaningful. We will have 90% power to detect a difference of this size, assuming an alpha of 0.05 and standard deviation of 8 (30-31).

9.2 Planned recruitment

We are aiming to recruit 50 dental practices and 530 participants in total.

9.3 Internal Pilot

An internal pilot stage has been included. The internal pilot is primarily designed to demonstrate that recruitment is possible and at the rate in line with our estimated milestones and costs. The specific objective is to assess the recruitment of practices and participants and monitor compliance with the clinical protocol and acceptability for patients and clinicians. Recruitment and acceptability will be explored using qualitative interviews (see section 7.8.1). During the internal pilot we are proposing a single decision point at the end of practice recruitment and 6

months participant recruitment. At this point we project 50 sites should be recruited along with 107 participants.

The progression criteria will be assessed based on traffic light system of green (proceed), amber (review, identify remediable factors and submit recovery plan to HTA with new targets for the following 6 months) and red (stop) as follows:

- Recruitment
  Green: 100% target recruitment achieved (107 patients; 50 dental practices)
  Amber: 50-99% recruitment achieved (54 patients; 25 dental practices)
  Red: less than 50% recruitment achieved (fewer the 54 patients; 25 dental practices)

- Fidelity with intervention
  Green: more than 75% of FP and RCTx interventions delivered as intended
  Amber: 50-75% of FP and RCTx interventions delivered as intended
  Red: less than 50% of FP and RCTx interventions delivered as intended

9.4 Statistical analysis plan

Demographic and baseline characteristics will be summarised and displayed in tables for all randomised participants by randomised treatment using appropriate summary statistics(i.e., mean (standard deviation) or median (percentile 25 – percentile 75) for continuous variables, and number (percentage) for categorical or binary variables). All study analyses will be done according to a pre-specified statistical analysis plan that will be agreed by the Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC).

9.3.1 Summary of baseline data and flow of patients

Baseline data will be summarised as described above. The flow of participants will be presented as a diagram following recommendations from CONSORT for non-inferiority trials (32).

9.3.2 Primary outcome analysis

The primary clinical outcome, clinical success at 1-year post-randomisation, will be analysed using a generalised linear model with a random effect for dentist and adjusted for minimisation covariates. The treatment effect will be summarised with treatment estimates and a 95% confidence interval. We will use the lower bound of 95% confidence interval around the absolute risk difference to exclude the pre-specified non-inferiority margin of 12%. An intention-to-treat analysis will be used as the primary analysis since this is a pragmatic study and the main interest is in the effect of allocating the treatments on participant outcomes (33).

The primary patient reported outcome will be analysed testing a superiority hypothesis, using an intention-to-treat framework, with a generalised linear model with the appropriate link function for the outcome distribution. The model will include a random effect for dentist and will be adjusted for baseline score and minimisation covariates.

9.3.3 Secondary outcome analysis

Secondary clinical outcome will be analysed following the primary clinical outcome analysis strategy as outlined in 9.3.2 under a non-inferiority hypothesis.
Secondary patient reported outcomes will be analysed following the primary patient reported outcome analysis strategy as outlined in 9.3.2. testing a superiority hypothesis.

The outcomes will be analysed using generalised linear models (using the appropriate link function for the outcome distribution). Models will be adjusted for minimisation covariates and baseline scores where available, and include a random effect for dentist. Treatment effects will be estimated using a treatment-by-time interaction, where applicable, and presented with 95% confidence intervals.

9.4 Subgroup analyses

Subgroup analyses on the primary outcome will explore the possible modification of treatment effect by the minimisation variables (excluding site) and country. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses

9.5 Adjusted analysis

Analyses will be adjusted as indicated above.

9.6 Interim analysis and criteria for the premature termination of the trial

There are no planned interim analysis.

9.7 Participant population

Adults (16 years and older) with symptoms indicative of irreversible pulpitis [as defined by ESE (10)] in a pre/molar tooth with deep caries and or a deep restoration. The main analysis for the primary clinical outcome will follow an intention-to-treat approach and, therefore, include participants as randomised.

9.8 Procedure(s) to account for missing or spurious data

We will impute baseline missing data for all analyses following best practice recommendations (34). For the primary analysis, we will undertake sensitivity analyses exploring patterns of missing data and consider how robust the findings are using multiple imputation approaches under an assumption of missing at random, and pattern mixture models if relevant (35).

9.9 Other statistical considerations.

Since our main framework of analysis, intention-to-treat, can produce more conservative results in non-inferiority trials (33), we will also present per-protocol analyses for compliance with randomised allocation (reported by the dentist) and clinical fidelity (see section 7.7.4 for more information). To support interpretation of results, we will follow recommendations for non-inferiority trials to present data on non-adherence according to participant's characteristics (33).

9.10 Economic evaluation

A full economic evaluation will be conducted. This will include a study-based analysis at one-year follow-up and a decision model to assess economic value over an extrapolated lifetime horizon. The primary economic outcome will be net benefit, WTP – cost (NHS and patient perspective) evaluated in a Cost-Benefit Analysis (CBA) framework. CBA is chosen as the preferred framework because of concerns that generic QALY measures are not sufficiently sensitive to capture the value of important outcomes in dental care. Cost Utility Analysis (CUA), cost per QALY, will also be conducted as a secondary economic analysis to comply with NICE guidelines for technology appraisal.

9.10.1 Estimation of costs

Costs will be estimated from both an NHS and patient perspective. NHS costs of providing the intervention and control will be based on the appropriate tariff costing in the respective regions of the UK. Contract payments are likely to vary over time, may not explicitly exist for FP, and may not capture the full opportunity cost of time and materials spent delivering the interventions. We will therefore use a micro-costing approach to cost the actual value of resource use displaced by delivering different interventions. To avoid duplication of reporting, micro-costing of consumables and resource usage will take place at the dental care professional level, rather than the participant level. Resources likely to vary by participant (such as procedure time, materials used) will be collected at the participant level using CRFs. Resource use data will be collected as described in Section 7.7.3 and will be costed at the patient and regional level, with aggregated average per patient costs used for the economic evaluation. Incremental costs per patient for FP compared to RCTx will be estimated using generalised linear models with appropriate distributions for cost data and adjustment for baseline covariates, such as gender, age, and smoking status. The costing analysis will include a statement on budget impact.

9.10.2 Estimation of benefits

WTP for the CBA will be elicited from a DCE. The DCE will be conducted with a nationally representative sample of the UK general population, using online panel surveys. The DCE will value intervention delivery characteristics (e.g., length of waiting time for treatment, number of visits required to the dentist) and patient relevant outcomes (e.g., need for re-treatment of the tooth) collected in the study. The valuation exercise will also be used to assess the acceptability of FP and predict uptake. The target sample size for the DCE (N=1,067) is calculated using Dillman, 2007 (36), using an estimate of the population of interest (i.e., the UK general adult population) = ~52 million), a conservative estimate of variation in the answers for the question of interest of 0.5, and an assumed margin of error of 3% in line with public opinion research, with a confidence level of 95%. A further sample of 100 respondents will be sought for a pilot study of the DCE. As a secondary objective, we will measure benefits in terms of QALYs gained, based on patient responses to the generic EQ-5D-5L health related quality of life measure, collected at baseline, 7 days and 1-year post-randomisation. We will also explore the feasibility of using OHIP data to inform a condition specific QALY measure.

9.10.3 Within trial economic evaluation

Costs and benefits will be combined to estimate incremental net benefit (WTP – costs) and incremental cost per QALY gained for FP vs. RCTx (37). The CBA results will be presented on a cost-benefit plane, illustrating the probability that FP is associated with positive or negative

incremental net benefits. The CUA results will be presented using cost-effectiveness acceptability curves (CEACs) and scatter plots on the cost-effectiveness plane. Sensitivity analysis will explore the impact of missing data and assumptions regarding costs on the cost-effectiveness outcomes. Specifically, we will explore the impact of considering NHS costs according to current payment structures vs. the opportunity costs of dentist's time for delivering the respective interventions. Subgroup analyses by country will also be conducted.

9.10.4 Decision Modelling

A tooth-level Markov decision analysis model will be developed to extrapolate study outcomes over a life-time horizon (38-39). The model structure and health state definitions across the disease pathway (e.g., treatment failure requiring retreatment and progression to tooth loss) will be developed in consultation with dental health professionals, patient experts and decision makers. National cohort datasets, such as the adult dental health survey, the control arm of the study, and data from our other NIHR funded trials (REFLECT, SCRIPT, INTERVAL and IQuaD) will be used to source baseline transition probabilities. Survival analysis will be conducted to estimate the baseline transitions over the lifetime of a tooth. Relative effects will be obtained from the clinical study data and supplemented with further literature reviews where necessary.

Health state costs will be sourced from the study data and routine data sources (ISD / BSA) for appropriate treatment in the respective model health states. NHS and patient perspective costs will be reported. Benefits in terms of WTP will be sourced directly from the general population DCE for specific health states (e.g., WTP to avoid treatment failure, tooth loss). The model will be configured to report both cost-benefit and cost-utility analyses. The model development began during the feasibility stage to ensure all relevant data are collected within the study.

The model will be fully probabilistic, and all assumptions will be extensively tested using sensitivity analyses. Key gaps in the evidence base will be identified and their potential impact on efficiency (net benefit) explored. Results will be presented on the cost-effectiveness and cost-benefit planes and using cost-effectiveness and cost-benefit acceptability curves to illustrate the probability that FP is associated with positive or negative incremental net benefit. Study participants will be consented to obtain longer term data linkage to routine records to validate the longer-term modelling assumptions and to update the model parameters over time. Value of information analysis will be undertaken to determine the value of future research and Expected Value of Partial Perfect Information (EVPPI) will help define future research priorities.

9.11 Process Evaluation

A mixed-method process evaluation will complement the study's evaluation of outcomes and examine implementation, mechanisms of impact and context as per MRC guidance (28):
Implementation: the process through which FP as compared to RCTx are delivered in dental practices, how this differs between dentists, the influence of the training received, fidelity and adaptation of the clinical protocols and the resources used, including the properties of the dental materials themselves, their cost and the definitive restorative approaches chosen.

Mechanisms of impact: how the intervention is received by patients (acceptability) and how dentist/patient interactions influence approaches to the management of irreversible pulpitis and any unintended effects of dentists using FP.
Context: through examining how external factors including national and local dental contractual arrangements, provision of private treatment, the influence of undergraduate and postgraduate and referral patterns to specialist dentists influence the delivery of the intervention and its outcomes.

The process evaluation will involve analysis of study outcomes data (including CRFs) and qualitative interviews with patients, dentists and other stakeholders such as managers of corporate bodies and dental service commissioners. Purposive sampling of patients for interview will be used to ensure a range of participants in terms of age, patterns of dental attendance and their experience of symptoms following the interventions. Dentists will be purposively sampled based on the types of dental contract they are working under, previous experience of differing approaches to managing irreversible pulpitis and levels of engagement with the study. The interviews will be guided by the theoretical domains framework (TDF) which has been used previously in implementation research to understand the motivations, cognitions and behaviours of dental professionals when implementing evidence-based practice (40-41). The interviews will be audio-recorded and transcribed verbatim. Framework analysis will be used and will involve the following stages: identifying initial themes, labelling the data, sorting the data by theme and synthesising the data. The analysis will be conducted by an experienced research associate with support of the PPI co-applicant. In addition, during the analysis, regular meetings will be held between the research team to discuss the emergent themes and consider the implications of these for the results of the outcome evaluation.

9.11.1 Qualitative Interviews
As part of the process evaluation, qualitative interviews will be conducted with dentists and patient participants who have taken part in the study to explore the experience of delivering the interventions, recruitment of participants to the study and acceptability of the interventions. If recruitment is below target following the internal pilot, interviews conducted up to this point will contribute to the refinement of the study recruitment strategies. Interviews may also take place with other stakeholders such as managers of corporate bodies and dental service commissioners.

For patient participants, the qualitative interview is an optional part of the study. Patient participants will have the option to consent to the interview as part of consenting to the study. The research team will interview a sample of these patients, where possible taking account of age, responses to the follow up questionnaire. If a patient participant gives their consent, and is selected to take part in an interview, the patient will be contacted approximately four weeks after randomisation and a suitable date and time for a remote qualitative interview will be arranged. The interview will be conducted by an experienced researcher.

A sample of dentists will be invited to take part in an interview. Dentists will be contacted directly by the qualitative research team, informed about the qualitative study and invited to take part in a remote interview at a convenient time. The research team will aim to sample dentists based on the types of dental contract they are working under, previous experience of differing approaches to managing irreversible pulpitis and with different levels of recruitment, in order to

capture a range of experiences. Dentists will be asked to consent to take part in an interview. Any additional stakeholder interviews will be arranged and conducted in the same way as dentist interviews. The interviews will be guided by topic guides developed from the literature and other dental studies. The topic guide for dentists will be guided by the Theoretical Domains Framework (42) and focus on delivering the intervention, acceptability of the intervention and recruitment. The topic guide for patient participants will be informed by the Theoretical Framework of Acceptability (43) and focus on experiences of recruitment, the intervention as experienced, and acceptability of both interventions. Where necessary, topic guides for other stakeholders will be developed based on the needs of the process evaluation (i.e., to contribute to establishing processes of implementation, mechanisms of impact and context). The topic guides will be used flexibly based on an iterative approach to data analysis to capture views and experiences related to study recruitment and all components of the process evaluation. Interviews will be audio-recorded and transcribed verbatim by an external company (Dictate2Us). The interviews will be analysed using Framework Analysis (44) (see Section 9.11).

10 DATA MANAGEMENT

10.1 Data collection tools

An anonymised screening log has been created for the purposes of providing an in-practice screening and monitoring tool that may be used to support practices if required. It will not be formally collected by the Study Team and the information held in the screening log will not be recorded. No participant identifiable data will be recorded.

10.2 Data handling and record keeping

CRF data will either be entered into the secure PIP database directly by the designated team members working in each site or sent to the Study Office for data entry depending on practice circumstances. Staff in the Study Office will work closely with the team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks by the Study Office will further enhance the quality of the data. Couriers will be used for the transportation of data between the sites and the Study Office.

10.3 Retention of data

Personal data will not be retained any longer than is required for the purpose for which they have been collected (10 years) and will be stored in compliance with the Sponsor's standard operating procedures. We will explore long term follow up of the whole cohort of participants. Documents will be reviewed by the CIs before being destroyed. We plan to seek consent to allow collection of long-term data on restoration longevity and health resource usage.

10.4 Access to Data

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agree to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

10.5 Archiving

The Sponsor is responsible for ensuring that study data is archived appropriately. All essential data and documents (electronic and hard copy) are retained for a period of at least 10 years after close of study according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs.

11 MONITORING, AUDIT & INSPECTION

11.1 Project management

University of Dundee will sponsor the PIP Study. An independent Trial Steering Committee (TSC) and an independent Data Monitoring and Ethics Committee (DMC) have been convened.

The role of the TSC is to monitor and supervise the progress of the PIP Study. The TSC membership consists of an independent Chair and other independent members, two PPI representatives and the Chief Investigator (CI). The NIHR HTA will be invited to nominate a representative to sit on the TSC. Other members include the grant holders. Observers may also attend, as may other members of the Project Management Group (PMG) or members of other professional bodies at the invitation of the Chair.

The DMC is independent of the TSC and study co-applicants. It will monitor accumulating PIP Study data during the course of the study and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the Protocol or closure of the Feasibility Study. It is anticipated that both TSC and DMC will meet at least annually during the Study.

The CI, all PIs, study co-ordinators, research dentist and nurse, and study personnel have undertaken any required GCP training.

The study will be supervised by a PMG. The chair of this group will be the CI and will consist of grant holders, representatives from the Study Office and CTU. The PMG will meet at least monthly however in the setup stages this may be more frequent. In addition, the PMG will also meet at the annual Trial Steering Committee meeting.

The Study Office will be based in the Dundee Dental School at the University of Dundee and will provide day to day support for the clinical centres and sites and through the Trial Manager and administrative positions who will provide a hub for dissemination of administrative and clinical support activities for the study. At each of the clinical centres, the co-investigators will be responsible for clinical training and liaison with local practices.

The Trial Manager based in CHaRT (Aberdeen) will take responsibility for supporting the regulatory requirements (e.g. submitting any amendments to REC or local approvals) and the day to day transaction of study activities (e.g. central monitoring of recruitment activities or producing reports for the PMG).The Trial Manager, Trial Administrator and Trial Administrative Assistant at the Study Office Dundee will take responsibility for the day to day collecting, collating, handling and entering data. These activities will be supported by the CHaRT Clinical Trials Unit at University of Aberdeen.

The programmers at CHaRT will create, maintain and update all applications programmes for the PIP Study. These study staff will be supported by CHaRT senior team: the CHaRT director, the Senior IT manager who will oversee all IT aspects of the study, while the Senior Trials Manager will provide mentoring and guidance to the Trial Manager and advice to the team on generic coordination issues. The Quality Assurance Manager will be responsible for advising on assessments of quality of the study, appropriate training of standard operating procedures, and will assist with any external monitoring and auditing of the study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with the principles of GCP.

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

A Research Ethics Committee (REC) favourable opinion, HRA (Health Research Authority) approval and NHS R&D approvals will be sought. The PIP Study will be conducted according to the principles of GCP provided by Research Governance Guidelines. A final report for the Study will be submitted to the funder, Sponsor and the relevant REC within the timelines defined in the regulations.

The PIP Study will run under the auspices of the Study Office in Dundee Dental School & Hospital and CHaRT in the University of Aberdeen. CHaRT is a fully registered Clinical Trials Unit with expertise in running multicentre RCTs. Both institutions are committed to the highest standards of research governance and seek to conform to all relevant governance guidelines and codes of practice as detailed in the Research Governance Framework and ICH guidelines for GCP. As well as ensuring that research is conducted according to the requirements set out in these documents, all research will be conducted with the written agreement of the relevant Multi-Centre and/or the Research Ethics Committee(s), and/or other relevant ethics committee(s) before starting recruitment. The CI will ensure, through the TSC and Sponsor that, adequate systems are in place for monitoring the quality of the study and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the study.

A study Participant Information Leaflet (PIL) will be given to each potential participant to inform them of the anticipated risks and benefits of taking part in the study. In particular, the trade-offs between possible short-term benefits and long-term risks will be explained. Informed signed consent forms will be obtained from the participants in all practices, by an individual who is trained in GCP. Patients will be given sufficient time to accept or decline involvement and are free to withdraw from the study at any time.

12.1 Research Ethics Committee (REC) review & reports

Research Ethics Committee (REC) approval, HRA (Health Research Authority) approval and R&D approvals for the study will be sought before the study commences.

The main benefit of participating in this study is an altruistic one to improve care for patients with dental pain caused by inflammation of the pulp that would currently only be treated with complex, expensive RCTx or extraction. A potential risk for those receiving a FP is that it may

delay the need for RCTx resulting in lengthier duration of symptoms and dental treatment, but all failures would be expedited for remedy. Conversely if the intervention is successful, we will have enabled approximately 265 participants to avoid RCTx or extraction. The knowledge that one is superior in terms of clinical or cost effectiveness would be of benefit to patients, the NHS and society.

12.1.1 Ethical issues
The XXX Research Ethics Committee has reviewed this study. The study will be conducted according to the principles of Good Clinical Practice provided by Research Governance Guidelines.

12.1.2 Annual reporting
Annual progress reports, end of Trial declaration, and a final report are submitted to the Sponsor and funder within the timelines defined in the regulations.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12.2 Peer review
The Study Protocol will be reviewed by the Trial Steering Committee, the funder (NIHR HTA) and by the Research Ethics Committee. The justification for and the proposed study design have been peer reviewed by independent expert panels as part of the application process to the funder. This involved two rounds of review as well as post award revision.

12.3 Public and Patient Involvement
During the Study, patient and public perspectives will be included in several ways. The PPI planning, training and facilitation in the study will be guided by the Trial Manager with PPI expertise, incorporating public partners in the Health Services Research Unit (HSRU) Public Involvement Group and utilising the newly established Dundee Dental PPI forum and group. The Trial Manager will support the PPI partner on the Project Management Group to review and discuss patient facing materials, recruitment processes and other aspects of the study conduct and dissemination. A patient advisory group will be established and will meet at regular intervals throughout the study to give patient perspective. Additional PPI input will be provided by two PPI partners on the independent steering committee. The PPI lead and the HSRU Public Involvement Group will support researchers and PPI partners throughout the study to ensure meaningful and accessible involvement.

12.4 Regulatory Compliance
The Protocol and Study conduct will comply with the UK policy framework for Health and Social Care research (v3.3 07/11/17) and any relevant amendments.

12.5 Protocol compliance
Protocol non-compliances are departures from the approved protocol.

- prospective, planned deviations or waivers to the Protocol are not allowed and must not be used e.g., it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study Protocol

- accidental Protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- deviations from the Protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.
- All breaches are notifiable to the Sponsor, the Sponsor SOP shall be followed.

12.6 Notification of Serious Breaches to GCP and/or the protocol

If a serious breach of GCP or Protocol is suspected, this will be reported to the Sponsor Governance Office immediately.

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

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor will notify the REC in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach

12.7 Data protection and patient confidentiality

The CI and trial staff will comply with GDPR and all applicable dental/medical confidentiality and data protection principles and laws about the collection, storage, processing, and disclosure of personal data. A Data Impact Assessment will be written and agreed prior to any study related activities. The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and personal data will be managed in a manner designed to maintain participant confidentiality. Patients will be reassured that the data collected during the research is kept strictly confidential. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate Study staff only. Computers used to collate personal data will have limited access measures via usernames and passwords.
Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee, or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and study staff will not disclose or use for any purpose other than performance of the study, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated Study staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

All Co-applicants and oversight committee members (TSC and DMEC) will be asked to sign a competing interests form to confirm there are no conflicts of interest.

12.9 Indemnity

The University of Dundee is sponsoring the study.

Insurance

The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Where the Study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity

The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

12.10 Amendments

Approval for any amendment will be requested of the Sponsor who is required to categorise as substantial or non-substantial. No amendment will be made without the appropriate approvals. In the event that the CI needs to deviate from the Protocol, the nature of and reasons for the deviation will be documented and submitted to the Sponsor. If this necessitates a subsequent Protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office (e.g., HRA and NRSPCC) for review and approval.

12.11 Post study care

The PIP Study will be conducted in accordance with the Declaration of Helsinki.

The Declaration of Helsinki states that "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process" and that "in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions."
The protocol should describe any interventions, benefits, or other care that the sponsor will continue to provide to participants after the trial is completed and provide justification if continued

access to the trial treatment(s) will not be funded. See the link for guidance https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

12.12 Access to the final study dataset

The Study statistician will have access to the final study dataset and prepare reports for the Project Management Group, Trial Steering Committees and Data Monitoring and Ethics Committees. Study investigator requests for access to the dataset will be considered by the Trial Steering Committee.

13 DISSEMINATION POLICY

13.1 Dissemination policy

To safeguard the integrity of the Study, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG. Once the Study findings have been published, a lay summary of the findings will be sent to all involved in the Study. A study publication/authorship policy will be agreed at the first TSC meeting.

13.2 Dissemination and outputs

Dental caries is a common disease affecting the majority of the population and which dental practitioners treat throughout their day-to-day practice. This study investigates a treatment option identified as being potentially able to generate a significant cost saving for the NHS. We have found it to be of high interest to practitioners and patients. We will produce new knowledge which will be valuable for these and other key stakeholder groups both in the UK and internationally. The communication strategy will ensure that all stakeholder groups are updated throughout the study and aware of the study results.

Patients

We will work alongside our Patient Advisory Group and other PPI partners to ensure key individuals and organisations are appropriately targeted and will co-create strategies to actively engage patients and the public. Contemporary social media platforms in addition to other communication channels will be explored and used as appropriate at different stages of the Study.

NHS

The results of the Study will be communicated directly to all participating dental practices. Members of the team may speak about the study at national conferences for GDPs such as the British Dental Association conference, meetings and conferences of the Faculty of Primary Care Dental Practitioners and local practitioner meetings. Our experience of conducting the Feasibility and Study will be used alongside our successful approach of including participating practitioners to speak at meetings, giving them an opportunity to raise awareness of the rewards of research participation as well as increasing visibility of the PIP Study. We will produce clinical summary papers for clinician targeted journals.

Academic Community

Outputs will begin shortly after the study starts with publication of the study protocol and continue throughout the duration of the study. We will also target high impact journals and major conferences to present the ongoing work conducted in the study.

End of Study Dissemination Events
Final dissemination events will be organised to report on the study. This will include key stakeholders (e.g.- patients/national patient advocates, clinicians, NHS England-commissioners, GDP providers participating practices/participants) to deliver impact across wide audience.

The PIP Feasibility and Study will be an exemplar of how research evidence can enter a data ecosystem to reduce waste in research by decreasing the time taken from publication to translation into practice. Ensuring timely publication, updating relevant Cochrane reviews and liaising with guideline development groups and early conversations with policy makers in service and education will facilitate change to improve the adoption of the research findings. During the PIP Feasibility and Study information will be gathered about possible barriers and facilitators to implementation both from the patient and dental practice perspective. These will be communicated and discussed with groups responsible for policy change, education and guidance development during the Study period.

Members of the research team and PIP Steering Committee will disseminate research findings to the UK Chief Dental Officers, UK Health Departments and commissioners in NHS, Public Health England, NICE, SIGN and SDCEP. We will communicate directly with the British Dental Association, Faculty of General Dental Practitioners (FGDP), postgraduate deans and Royal Colleges.

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Appendix I: AUTHORSHIP POLICY FOR the PIP Study

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria[1]:

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged, and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. **Preferred CHaRT authorship**

Where possible, all CHaRT trials should publish using all the named contributors who qualify for authorship in the by-line i.e., Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using by-lines similar to “The XXXXX trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the XXXX trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by-line would read 'Jane Doe for the Trial Group') [2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. **Determining authorship**

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use

as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. **Ordering of authors**
The following rules may help with the ordering of authors, particularly for publications with individual authorship:
i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e., have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS
All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

4. DISCLAIMERS

Authors should also ensure they include the trial funder's disclaimer: refer to the funder's website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE
Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the PIP study, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial, should be peer reviewed by the Project Management Group. The Project Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the trial team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

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