Selective **C**aries **R**emoval **i**n **P**ermanent **T**eeth **Trial Protocol**

Trial Acronym	SCRiPT
Sponsor	University of Dundee
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Funder	This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference 17/127/07). 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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Version History	Description of change
Version 1. 30 OCT 2019	Original
Version 2. 17 DEC 2019	Add ability to provide informed consent to inclusion criteria in Summary/Synopsis and section 4.11. 4.11 Final inclusion criterion edited to be consistent with summary/synopsis to more explicitly indicate (for a dentist) that teeth should not have a crown or laboratory made restoration. Funding statement amended. Correct repetitious numbering of section 6.2. Table 3 edited to move consent from screening to initial treatment visit (baseline), replace reference to full mouth charting with DMFT, and rename table. Addition of REC name to section 11.1. Remove redundant placeholder text from section 12.2. Remove track changes.

VERSION 3. 29 JUNE 2020	Section 7.3: Changes to adapt processes for stakeholder interviews during COVID-19 pandemic where face to face contact may not be possible. Text edited to indicate some stakeholders might be interviewed twice with first interview taking place during the set-up phase to explore their expectations and any COVID-19 related issues. Text edited to indicate obtaining informed consent to include options of written, verbal (audio recording) and/or digital methods.
VERSION 4. 24 FEB 2021	Changes to adapt processes for participants and practices during COVID-19 pandemic. Edits to section on training to allow virtual training and feedback where face to face is not possible. Edits to participant selection and enrolment to apapt to local practices, participants and restrictions and allow aspects of discussion about the study to take place over the telephone between identification and initial treatment visit. Removal of mentions of telephone randomisation as this will take place on the website only. Removal of mention of cash payments to participants as these will be made with vouchers only.
VERSION 5. 13 May 2021	Removal of notes from page 1 Typographical: Inclusion of NPRS in table of abbreviations. Layout change in summary table so primary objectives/ outcomes are aligned and similarly secondary objectives/outcomes. Summary table: Inclusion criteria and secondary objectives edited to match main text. Table 1: economic outcome measures included Table 2: economic objectives edited for clarity 4.1 Additional clarification of protocol if pulp is exposed. 4.3 Typographical change to clarify masking 6.3.1 Additional section covering optional e-consent process for participants who opt to consent in this way. 7.1 Typographical change to clarify baseline data collection protocol 9. Typographical change to clarify economic modelling time-frame, DCE. Additional text on planned subgroup analyses Missing citations added
VERSION 6. 22 Nov 2023	Revisions to sample size, median follow-up time and planned trial period in the following sections: • Trial Summary/synopsis • Section 4.10 • Table 1 • Section 4.4 – flow-chart • Section 8.1

	Clarification on the strategies to assess compliance: • Section 7.5 Clarification on aspects of data collection • Time and travel questionnaires (section 9.1) • Follow-up dental visits (section 4.6) Other minor rewording in relation to the health economic secondary objective, capping of actively recruiting sites to 38, confirmation that participants can only be randomised once into the study, and clarification that outcome data is held by Public Health Scotland rather than the Information Services Division.
Version 7, 11 June 2024	Addition of clinic questionnaire for SCRIPT practice staff to hand out to participants attending for check-up or treatment (section 4.4 trial flow-chart; section 7.1, patient reported outcomes; table 3). Addition of strategies to maximise response rates to the time and travel questionnaire (section 9.1)

PROTOCOL APPROVAL

SCRIPT Trial

Signatures
The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Co-Chief Investigators	C Ramsay, J Clarkson Signatures	 Date
HSRU Director	C Ramsay Signature	 Date
Individual Responsible for Statistical Review	G MacLennan Signature	 Date

LIST OF ABBREVIATIONS

AE	Adverse Event
CCR	Complete Caries Removal
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trial Unit
DCE	Discrete Choice Experiment
DMC	Data Monitoring Committee
DMS	Data management system
EQ-5D-5L	EuroQOL five dimensions questionnaire
GCP	Good Clinical Practice
GDP	General Dental Practitioner
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ICF	Informed Consent Form
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
OMG	Operations Management Group
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NIHR	National Institute Health Research
NPRS	Numerical Pain Rating Scale
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
PPI	Patient and Public Involvement
PQ	Patient Questionnaire
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Selective Caries Removal

SD	Standard Deviation
SOP	Standard Operating Procedures
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

SUMMARY/SYNOPSIS

Trial Title	SCRIPT: **S**elective **C**aries **R**emoval **i**n **P**ermanent **T**eeth	
Trial Design	This is a pragmatic, primary dental care, multi-centre, single-masked, two-arm patient randomised controlled trial including an internal pilot, comparing the clinical and cost-effectiveness of Selective Caries Removal (SCR) with Complete Caries Removal (CCR) in permanent posterior teeth.	
Trial Population	NHS dental attenders aged 12 years and over who have deep caries in an adult pre-molar or molar tooth. The decision to include adolescents and younger adults is based on the high prevalence of primary lesions for this age group within the general population.	
Sample Size	Original sample size: 623 participants Update to sample size (2023): a minimum of 369 participants	
Planned Trial Period	Start date: 01.06.2019 End date: 29.02.2024 Revised end date (2023): 28.02.2026	
Follow up phase duration	Clinical outcomes: until end of trial (34 months median for primary outcome; up to 36 months for other clinical outcomes) Patient reported outcomes: up to 36 months	
Primary	**Objectives** • To compare the clinical effectiveness of SCR with CCR strategies on sustained tooth vitality. • To compare the costs and benefits of SCR with CCR over a modelled life-time horizon.	**Primary Outcome Measures** • Clinical: sustained tooth vitality with 34 months median follow- up. • Economic: incremental net benefit over a life-time horizon
Secondary	**Objectives** • To evaluate pulp exposure during caries removal, progression of caries, dental pain and need for dental pain relief, restoration failure and patient oral health-related quality of life. • To determine general population preferences for the type of treatment provided and outcomes of care; to determine short term costs and benefits up to 3-year follow-up. • To explore the implementation of technologies and the mechanisms of impact including acceptability of interventions to patients and clinicians.	**Secondary Outcome Measures** • Clinical: pulp exposure during caries removal; progression of caries; tooth-restoration failure and re-restoration • Patient-centred: dental pain; need for dental pain relief; health status; oral health-related quality of life; patient satisfaction; oral health behaviours •Economic: NHS and patient perspective costs; general population preferences; willingness to pay; incremental net benefits; QALYs and incremental cost per QALY up to 3-years follow-up.
Inclusion Criteria	Patients who are: (i) Aged 12 and over, suitable to receive either clinical procedure in the trial. (ii) Able to provide informed consent. (iii) Receiving some or all of their treatment under NHS Patients who have: (iv) One (or more) pre-molar or molar teeth with caries (primary or secondary) extending into the pulpal third of dentine.	

	(v) Lesion affecting proximal and/or occlusal surfaces and would be filled with a single direct restoration.	
Exclusion Criteria	(i) If the carious tooth shows signs or symptoms of irreversible pulp pathology or loss of vitality including: presence of a sinus, tenderness to percussion, buccal tenderness, pathological mobility, severe sensitivity or evidence of pathology on a periapical radiograph.	

1 INTRODUCTION

Dental caries in permanent teeth is a widespread and costly public health problem. Globally, it is the most prevalent non-communicable disease and can have serious health sequelae which can impact negatively on quality of life and productivity[1-5]. In the UK most adults experience dental caries during their lifetime and the 2009 Adult Dental Health Survey reported that 85% of adults have at least one restoration [6]. Although management of dental caries focusses on primary prevention, many individuals still require operative intervention involving removal of dental caries and placement of a restoration (filling). The removal of less tooth tissue for both primary and secondary caries (new and under existing restoration) reduces the risk of failure due to tooth-restoration fracture and the surfaces are less vulnerable to further caries[7]. Furthermore, smaller cavities make the placement of the more technique sensitive resin restorations easier and likely to last longer. However, despite the prevalence of this non-communicable disease there is no consensus about how much caries affected tooth tissue to remove prior to placing a filling to achieve optimal patient outcomes. This trial will use the term selective caries removal rather than partial as it reflects the consensus in terminology from an international group of 20 cariologists and restorative dentists which included several members of this team[8]. Evidence for selective compared to complete or near-complete caries removal suggests there may be benefits for selective removal in maintaining a healthy blood and nerve supply to the tooth (sustained tooth vitality) which avoids abscess formation and pain, so eliminating the need for more complex treatment or eventual tooth loss. However, the evidence is of low scientific quality and mainly gleaned from studies on children's primary (first) teeth.

2 BACKGROUND

The majority of current NHS treatment is managing failed restorations and their consequences moving to increasingly invasive and costly treatments. NHS expenditure on primary and secondary dental care in England approximates to £3.4bn per year, with over one million patient contacts weekly. Many of these contacts relate to treatment of caries. In 2016/17 in England, there were over 7m fillings, over 2m extractions and around 1.5 m endodontic treatments, crowns, inlays or bridges provided to adult NHS patients. The total value of these treatments was about £1.27bn, with a significant burden on both patients (~£635m) and the NHS (~£639m - £290m for fee-paying and a further £349m for exempt patients)[9] . A similar pattern of spend has been observed in Scotland for 2017[10]. This does not take into account the dental treatment provided in private practice.

For the management of large carious lesions the EU directive to phase down dental amalgam has implications too. Currently the majority of large cavities are restored with amalgam but since July 2018 this is not recommended for under 15 year olds[11]. The most common reason for referral to an endodontics specialist is failed molar root canal treatment from general dental practitioners. Molar root canal treatments are time consuming, costly and complex. In England one area commissioner has decided to no longer fund this treatment on the NHS meaning patients have the tooth extracted or pay privately. Therefore, there is a need to develop "modern dentistry techniques" which aim to preserve rather than remove excessive tooth tissue.

2.1 RATIONALE FOR THE TRIAL

The importance of this topic has been highlighted both by the patients and the general dental practitioners. General dental practitioners within the Scottish Dental Practice Based Research Network (http://www.sdpbrn.org.uk/) in 2011 voted this as the top research priority. More recently, focus groups and interviews with general dental practitioners followed by a national online survey of dental practitioners, which was conducted as part of this proposal, have established the current importance of the topic and informed the trial design of SCRIPT. The 320 survey participants demonstrated considerable variation in practice with 3% reporting they always perform selective caries removal and 13% reporting they never perform selective carious tissue removal. The primary outcome in the SCRIPT trial was considered to be important by 99% of participants and their free text comments clearly demonstrate the current professional uncertainty around how best to manage patients with deep carious lesions - "*would be willing to use selective caries removal if there was proof it does no harm" and "I'd be very keen to see more research in this area and would put it to use in my day to day practice."*

In this trial young people between the ages of 12 years and 15 years will be included because the 2013 UK child dental health survey reported, that nearly a half (46%) of 15 year olds and a third (34%) of 12 year olds had "obvious decay experience" in their permanent teeth[12]. Of these a fifth (19%) of 12 year olds and 15 year olds (21%) had decay into dentine requiring treatment. Toothache was experienced by 18% of 12 year olds and 15% of 15 year olds. This suggests that the burden of dental decay is very high in this group and

thus including this age group in the trial would generate evidence of acceptability and issues related to actual treatment provision. Such evidence would help the dental practitioners in primary care to adopt minimally invasive approaches to carious tissue removal especially when the recent EU directive has recommended not to use amalgam fillings in under 15 year olds[11].

This was further highlighted by a research priority setting exercise conducted with patients at a general dental practice in Derbyshire with the greatest potential benefit seen for the young people. A PPIE group at the Health Services Research Unit (HSRU) in Aberdeen thought development of such conservative techniques was very important as they could improve both the health and dental experience of patients. Overall, new evidence investigating whether a procedure involving sealing decay in stops the chances of teeth being lost and reduces the chance of painful episodes and further complex treatment like root canal treatment would be important and welcomed by patients.

Randomised control clinical trials and systematic reviews have concluded that SCR may offer benefits, but the evidence on managing deep caries in permanent teeth is weak and biased[13-16]. Schwendicke et al.[13] found a significant risk reduction for pulp exposure (OR 0.31 [0.19-0.49]), but pulp symptoms (OR 0.58 [0.31-1.10]) and risk of restoration failure (OR 0.97 [0.64-1.46]) were inconclusive (n=1,257). Similarly, for selective caries removal, Ricketts et al.[16] found a significant risk reduction for pulp exposure (OR 0.23 [0.08-0.69]), but again pulp symptoms (OR 0.27 [0.05-1.60]) and risk of failure were inconclusive (n=345 in the partial caries analysis of primary and permanent teeth). Quality of the evidence is judged to be poor scientifically and most of the included studies were conducted solely on children with short term follow-up[17-19], used less durable materials[18, 20] or included more aggressive CCR interventions to “hard” dentine[15, 21] than would be present in UK NHS.

Bjørndal et al.[14] followed-up for five years a 2-staged (stepwise) carious tissue removal protocol on lesions spreading into the pulpal quarter of dentine (n=239). Pulp exposure rate was lower in this stepwise removal protocol (21.2% vs. 35.5%; p = 0.014) and more successful (60.2% vs 46.3%) (p = 0.031) when pulp exposures were classed as failure. The trial has limited generalizability to SCRIPT’s context and patients: it recruited participants with more severe caries and its two interventions differed from SCRIPT’s. Their partial approach (2-step) was similar to CCR; their CCR approach was more aggressive than the one we propose to use, excavating “hard” dentine. Therefore, more evidence is needed about the performance of a minimally invasive option of SCR in the NHS and about whether dentists will adopt it. There is one ongoing trial in France[22] looking at this research question in a secondary care setting. Personal communication with the trial team confirmed they had experienced a merger (contamination) of the two technologies (i.e. the two techniques undertaken by an individual dentist tended to become more similar dependent upon their initial skills and preferences). The trial has had more than 30% loss to follow-up. The authors believe that is due to the secondary care setting where patients are usually transient and short term. Our research robustly monitors and minimises the risk of the technologies merging, and most patient participants are routine attenders at their dental practice.

Therefore, this research is important to establish whether SCR will sustain tooth vitality and reduce the need for complex, costly treatment including root canal treatment, crowns, extractions, bridgework or implants. In addition to cost savings this reduced treatment need would improve quality of life anxiety and stress.

The risk to participants is low as both treatments are utilised in NHS practice albeit that SCR is relatively under-employed. However, for SCR, which is a minimally invasive treatment, the perceived risk is the residual caries may lead to further treatment. The risks from CCR are already managed within existing dental practice so the trial does not impose any new risks. Risk in both arms will be monitored as part of the trial as the primary and some secondary outcomes directly measure the impact of each treatment (see section 4.7).

3 TRIAL AIM, OBJECTIVES & OUTCOMES

3.1 AIM

To compare clinical and cost-effectiveness of selective caries removal (SCR) compared to complete caries removal (CCR) in permanent teeth in NHS dental attenders aged 12 years and over who have deep caries in an adult pre-molar or molar tooth.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	Outcome Measure:	Timepoint of outcome measured
• To compare the clinical effectiveness of SCR with CCR strategies on sustained tooth vitality.	Clinical: Sustained tooth vitality	a median of 34 months
• To compare the costs and benefits of SCR with CCR measured to three years and extrapolated over a modelled life time horizon.	Economic: incremental net benefits	Modelled life-time horizon

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	Outcome Measure:	Timepoint of outcome measured
• To evaluate pulp exposure during caries removal, progression of caries, dental pain and need for dental pain relief, restoration failure and patient oral health-related quality of life. • To determine general population preferences for the type of treatment provided and outcomes of care; to determine short term costs and benefits up to 3 year follow-up. • To explore the implementation of technologies and the mechanisms of impact including acceptability of interventions to patients and clinicians.	**Clinical:** • Pulp exposure during caries removal; • Progression of caries; • Tooth restoration failure and re-restoration **Patient-centred:** • Dental pain (NPRS); need for dental pain relief; • Health status; Oral Health-Related Quality of Life • Oral health behaviours • Patient satisfaction **Economic:** NHS and patient perspective costs, general population preferences, willingness to pay, incremental net benefits, QALYs and incremental cost per QALY. Economic outcomes measured over 3 years	see Table 3 in section 7.1

4 TRIAL DESIGN

This is a pragmatic, primary dental care, multi-centre, single-masked, two-arm patient randomised controlled trial including an internal pilot, comparing the clinical- effectiveness and cost-benefit of Selective Caries Removal (SCR) with Complete Caries Removal (CCR) in permanent posterior teeth.

A flow diagram is provided in Section 4.4. Follow-up will last at least 3 years and will be conducted in multiple sites across the UK. The design includes an internal pilot to assess the recruitment of practices and participants and monitor compliance with the clinical protocol and acceptability for patients and clinicians (see section 7.4).

4.1 INTERVENTION

The interventions being evaluated, SCR and the best alternative CCR, differ solely in the amount of carious dentine removed during the excavation phase of restorative treatment of deep dental caries. Clinicians will restore the tooth with the material that they would normally use. This may be amalgam or resin composite with or without glass ionomer cement. Placement of a lining is permitted. However it should not be medicated i.e. including steroids or antibiotics. If the pulp is exposed, usual care will be provided and recorded. Information about any pulp protection material placed will be recorded.

4.1.1 Intervention: Selective caries removal (SCR)

- Gain access to the dentine caries by removing superficial enamel or existing restoration
- Remove caries from the periphery of the cavity to allow for good adaptation and seal to the restoration either at the enamel dentine junction or the peripheral 2mm of dentine if the cavity margin is on root dentine.
- Remove remaining carious dentine to soft dentine "that deforms when an instrument is pressed into it and can be easily scooped up (e.g. with a spoon hand excavator) with little force being required"[8].

4.1.2 Control: Complete caries removal (CCR)

- Gain access to the dentine caries by removing enamel or existing restoration
- Remove caries to firm dentine "physically resistant to hand excavation and some pressure needs to be exerted through an instrument to lift it" [8].

4.2 TRAINING IN THE DELIVERY OF INTERVENTION

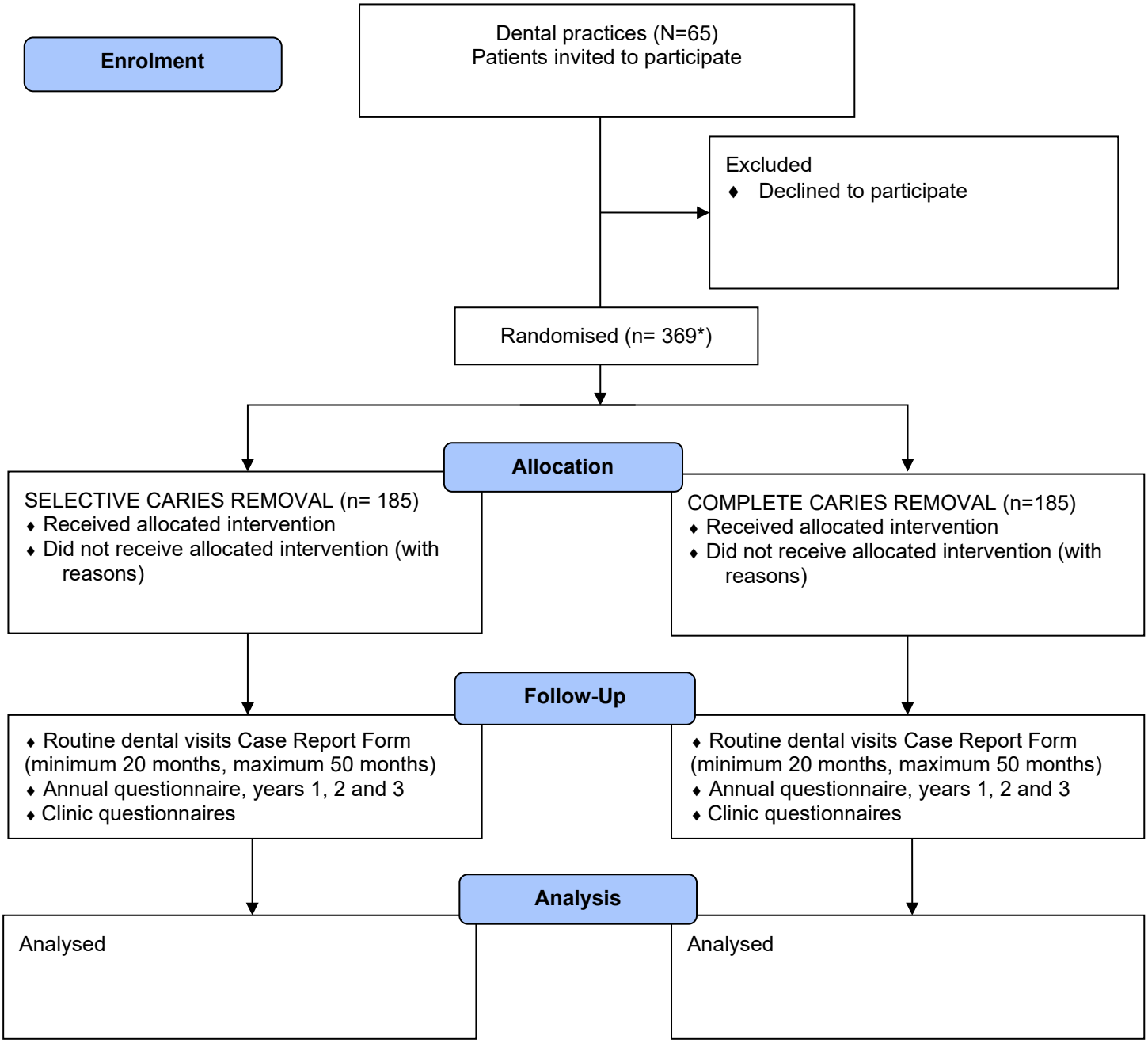
As the primary difference between the health technologies being assessed is the amount of carious dentine removed effective clinical training is of prime importance. The training will utilise a novel clinical learning tool, providing an on demand online resource and mechanisms for monitoring sustained delivery of the allocated technology.

All clinicians will participate in and complete the SCRIPT trial training (Part 1 hands-on in clinical procedures & Part 2 Good Clinical Practice). Other members of the dental team will complete SCRIPT Part 2 which can be delivered remotely. Part 1 will be provided in hands-on clinical facilities where COVID restrictions allow. Alternative Part 1 remote training and feedback will be provided if face-to-face meetings are not permissible.

4.3 TRIAL DESCRIPTION

SCRIPT is a pragmatic, primary dental care, multi-centre, participant-masked, two-arm patient randomised controlled trial including an internal pilot, comparing the clinical and cost-effectiveness of Selective Caries Removal (SCR) with Complete Caries Removal (CCR) in permanent posterior teeth in participants aged 12 years and older.

4.4 TRIAL FLOWCHART



*This is the minimum number of participants required. We plan to continue recruitment until the end of January 2024 to increase the sample size and power of the study, this is particularly important as some participants will not have the full 3 years of follow-up.

4.5 TRIAL MATRIX

See Table 3 in Section 7.

4.6 TRIAL ASSESSMENTS

Trial assessments will occur at baseline, at the time of interventions/routine dental visits, in annual questionnaires and at the end of their follow-up if applicable (for participants that did not attend any interventions/routine dental visits during their follow-up). See Table 3 in Section 7.1.

4.7 TRIAL SAFETY ASSESSMENTS

A potential risk is that some participants may have failed restorations that then need recovery using conventional approaches of complete or near complete caries removal before filling and may require a larger restoration than initially intended. During any restoration failure participants may experience discomfort but all failures would be expedited for remedy. Prior to obtaining consent all the participants will be informed of the potential risks and benefits of both the treatment procedures using a patient information sheet developed in collaboration with the PPI co-applicants, PPI@HSRU group and in line with guidance from the HRA. The risks and benefits will also be discussed by the patient's own clinician as part of the process of obtaining informed consent.

During the trial participants will be monitored regularly as per the study time points. It is made clear to both the patients and their clinicians that, within the design of the study, patients may attend anytime a dental appointment is needed. An additional visit may be requested if a participant has not received any post-intervention visit by 4 months from end of the follow-up period. No dental treatment, whether delivered in the dental surgery or following referral to specialist services will be withheld from patients as a result of taking part in this trial.

4.8 INCIDENTAL FINDINGS

We consider the risk of unknown pathology is extremely low. Any incidental findings (i.e. previously undiagnosed condition) considered to be clinically significant will be reported according to routine clinical practice. If radiographs reviewed by two independent/trial clinicians identify pathology other than routine dental disease, trial staff would contact the participant's general dental practice.

4.9 TRIAL POPULATION

NHS dental attenders aged 12 years and over who have deep caries in an adult pre-molar or molar tooth. The decision to include adolescents and younger adults is based on the high prevalence of primary lesions for this age group within the general population.

4.10 NUMBER OF PARTICIPANTS

The trial will aim to recruit 65 practices (each recruiting an average of 10 participants) to achieve the target of 623 participants over the 18-month recruitment period (Figure 1). The 18-month recruitment period allows for a staggered site set up and lower recruitment during peak holiday times (Christmas and summer) and during last few months of the recruitment period. Based on our experience of other dental studies, we anticipate that there will be a variety of approaches to recruitment undertaken by dental practices – some will recruit in weekly cohorts; others will be over a few months. We have estimated that 25% of eligible participants will be recruited.

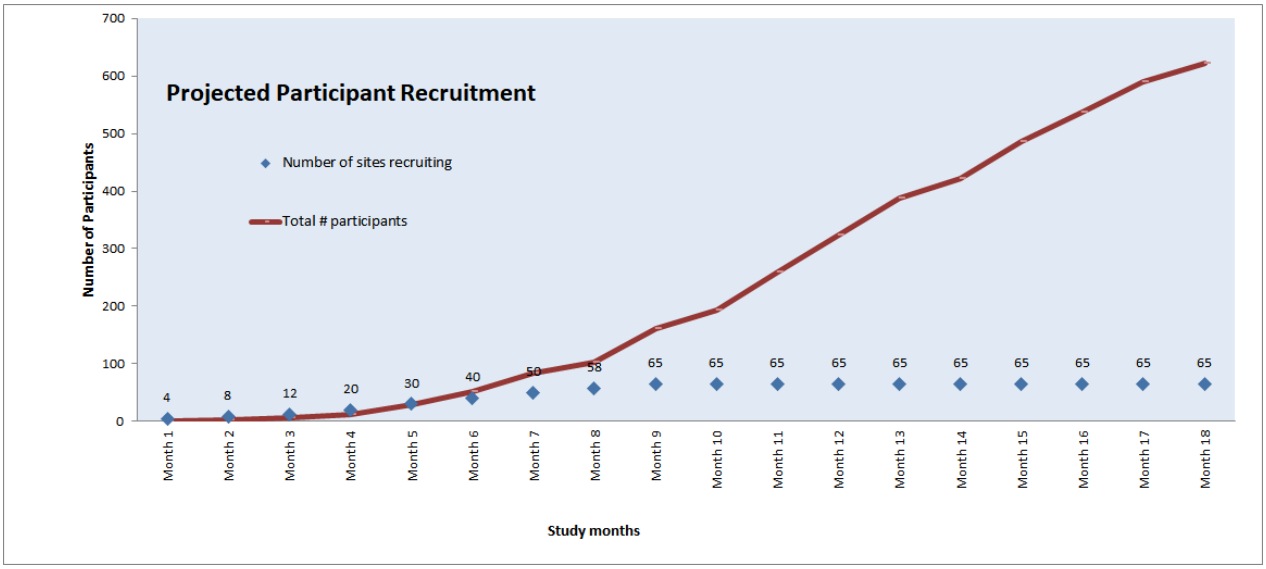


Figure 1: Projected participant recruitment and number of sites recruiting across the 18-month recruitment period.

UPDATE (2023)
As per advice from the funder, the number of actively recruiting sites will be capped at 38. The revised target number of participants is 369. This is the minimum number of participants required; however if this number is reached before the end of January 2024, we propose to continue recruiting beyond this target. The study is event-based, and over-recruitment will help compensate that some participants will not have a full three year follow-up within the study.

4.11 INCLUSION CRITERIA

- Aged 12 years and over, suitable to receive either clinical procedure.
- Patients able to provide informed consent
- Patients receive some or all of their treatment under NHS
- One (or more) pre-molar or molar teeth with caries (primary or secondary) extending into the pulpal third of dentine.
- Caries may be proximal and/or occlusal and the lesion will be suitable for a direct filling with a single restoration.

4.12 EXCLUSION CRITERIA

- If the carious tooth shows signs or symptoms of irreversible pulp pathology or loss of vitality including the presence of a sinus, tenderness to percussion, buccal tenderness, pathological mobility, severe sensitivity or evidence of pathology on a periapical radiograph.

5 DENTAL PRACTICE RECRUITMENT

General dental practice is the main provider of NHS dental care. SCRIPT will recruit approximately 65 NHS dental practices (and up to 75 clinicians) from across the UK. A list of participating practices will be kept up to date and provided on the public trial website: https://w3.abdn.ac.uk/hsru/script. In addition to independent NHS dental practices we will include corporate NHS dental practices to account for the increase in the trend for high street corporate bodies. BUPA Dental Services have formally given permission for up to 30 of their NHS practices to be involved - they currently have approximately 400 primary care practices across the UK. These practices provide routine NHS care.

The SCRIPT trial will be open to all general dental practices with NHS patients in the participating regions. An open invitation will be distributed using routine NHS communication systems such as NHS Education for Scotland's Portal and BUPA newsletters to request expressions of interest. Practices that have successfully recruited to and delivered previous dental HTA trials will be targeted through our research networks. Also, the planned NIHR Clinical Research Network oral and dental specialty national questionnaire will be used to identify interested practices. 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. A lead clinician per practice will be responsible for the trial and to oversee that the protocol is adhered to and more than one clinician per practice may participate. Digital X-ray facilities at the practice will be preferred but are not essential.

UPDATE (2023)
As per advice from the funder, the number of actively recruiting sites will be capped at 38.

6 PARTICIPANT SELECTION AND ENROLMENT

6.1 IDENTIFYING PARTICIPANTS

Local procedures at the participating dental practices and the mode of approach to potential participants will vary to accommodate both the variability at sites and the needs of potential participants. Trial clinicians will identify patients at routine visits that meet the inclusion criteria and explain the trial. Eligible patients who express interest will be given or sent a participant information leaflet, consent form and baseline questionnaire and an appointment for their treatment as per current clinical practice. Prior to or at the treatment visit the patient will be given the opportunity to clarify any questions prior to written consent being obtained.

6.2 SCREENING FOR ELIGIBILITY

The eligibility of all participants will be assessed and determined by their dental practitioner following clinical and radiographic examination. If more than one tooth is eligible, a trial tooth will be selected at random (see section 6.5).

6.3 CONSENTING PARTICIPANTS

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. Potential participants will be given a trial information sheet detailing the process and procedures of the trial, and the risks and benefits of the interventions to be tested when attending a routine visit at their dental practice. Existing patients with known caries will be eligible to be approached and will be sent a participant invitation letter in addition to the trial information sheet. Informed signed consent will be sought prior to or at a subsequent treatment visit and obtained using a standardised consent form by the participant's clinician who will be appropriately trained. Participants will be given sufficient time to accept or decline involvement and will be free to leave the trial 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. Depending on local processes and COVID restrictions aspects of this discussion may also take place over the phone between appointments. Potential participants may make a decision to participate when they attend for their initial treatment visit or alternatively at home prior to the initial treatment visit after telephone counselling. Participants who decide to participate following telephone counselling can either send their completed documents (consent form and baseline questionnaire) through the post or return them at their baseline appointment. The participants will be asked to consent to: participation; randomisation; follow up; contact in the future about this and other relevant research (which includes the qualitative interview); electronic tracing using NHS data (and if relevant BUPA data); data linkage with routine NHS data sources; and anonymised sharing of data for future research.
Participants will receive £30 in high-street vouchers for participating in the trial – half following recruitment and half at the end of follow-up. This will be posted to them by the trial office following the baseline visit.

6.3.1 Obtaining e-Consent

To cater for participant preference and COVID adaptations, participants may opt to consent using an e-consent form via the secure web-based trial management system provided by CHaRT. If this option is preferred, participants can give their email address to the site at the screening stage which is entered into the secure web-based trial management system. Participants will first be sent a verification email with a link to verify their email. Once the 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 has identical wording to the paper form, with PIL version automatically populated and with participant signature given via a signature box which can be signed using a finger tracing via a touch screen or using a mouse. Should participants consent using e-consent this may be at any time prior to the treatment visit. Clinician countersignature will be recorded on the e-consent only after discussion has taken place with the participant about the study and any participant questions have been answered. Only once both patient and clinician signatures are present will informed consent be considered to have been obtained. 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.

Should participants who are sent the study information not choose to take part in the study their email address 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.

6.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

A log will be maintained of patients who were approached about the trial 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.

6.5 RANDOMISATION

6.5.1 Randomisation

Randomisation will be at patient level. Eligible and consenting patient participants will be randomised to one of two intervention groups using the proven 24-hour web-based application, hosted by the Centre for Healthcare Randomised Trials (CHaRT). The randomisation algorithm will use recruitment site, number of eligible teeth (1; >1) and type of caries (primary and secondary) as minimisation covariates to allocate to treatment intervention and control groups in a ratio of 1:1. A random element will be incorporated into the randomisation algorithm. If the person has more than one eligible tooth, a trial tooth will be selected at random (the index tooth) by the randomisation application. The person with delegated authority will access the web-based system. Patient screening identification initials, recruiting site and eligible teeth will be entered into the web-based system which will return the allocation status. To maintain participant blinding, participants will not be informed of their allocated treatment group following randomisation. Participants can only be randomised once to the study.

6.5.2 Intervention Allocation

The person with delegated authority will be informed of the allocation immediately. Should they not be the clinician performing the intervention they will inform the clinician of the allocation. In addition, a separate confirmatory email will inform the trial office, the site principal investigator and other delegated individuals at the site of the allocation. The participant will not be informed.
All eligible teeth will be treated in the same way. All other carious lesions after baseline will be treated as the clinician prefers. This will be recorded on Case Report Forms (CRFs) so appropriate sensitivity analyses can be completed at the end of the trial.

6.5.3 Change of Status / Withdrawal procedures

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 is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal is retained and used in the analysis.

If participants wish to withdraw from the trial they will be asked if they wish to withdraw from all trial activity, from receiving treatment or from completing questionnaires. For participants who withdraw from active trial follow-up routine follow-up data from GDP records will be used for trial purposes unless the participants explicitly withdraw permission.

Participants who lose capacity to consent during the study will be withdrawn. 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 DATA COLLECTION & MANAGEMENT

7.1 DATA COLLECTION

Baseline characteristics
At baseline socio-demographic characteristics of age, gender and eligibility for free dental treatment will be recorded at the time of the initial treatment visit. Prior to treatment, baseline health related quality of life (EQ-

5D-5L)[23], oral health-related quality of life (OHIP-14), related oral health behaviour (type of toothbrush, brushing twice a day for 2 minutes, frequency of interdental cleaning, behaviour after brushing) will be collected through a paper or online patient questionnaire depending on participant preference. Oral health status and caries experience (DMFT) will be calculated from a full mouth charting by the clinician. Bitewing radiographs and periapicals' (if clinically needed) will be collected as part of routine care but copies will be provided to the trial team to provide a measure of the extent of caries and confirm exclusion of signs of pulp pathology. A CRF will record the details of treatment including caries removal, restoration placed and resource use required to deliver the respective treatments.

Clinical outcomes: Recorded on the CRF completed by the clinician at all visits until the end of the trial. It will record clinical and participant-reported signs and symptoms of tooth pain, the findings of any radiographs taken, the reason for and detail of any dental treatment provided for included teeth. Radiographs taken during the trial will be according to good practice guidelines based on caries risk at intervals between 6 and 24 months. Clinicians will take a bitewing radiograph at the one year post-treatment, in accordance with FGDP Guidelines[24] since included patients are considered at high risk, at the follow-up visit and the trial team will request a copy for treatment adherence monitoring (see section 7.4) . If a participant has not received any post-intervention visit by 4 months before the end of their follow-up period, they will be contacted to ascertain current oral health and offered an appointment. All radiographs will be assessed by a clinical researcher who is blinded to treatment allocation. Digital x-rays will be forwarded via the secure trial management system and digital images of wet films made.

Sustained tooth vitality will be collected at routine dental visits, recorded in the CRF and used in a time-to-event framework defined as the time from randomisation to root canal treatment or extraction due to loss of vitality, the primary time point of interest is three years. Sustained tooth vitality will be determined by the absence of root canal treatment or extraction due to loss of vitality and the absence of clinical signs and symptoms of pulp death including evidence from radiographs.

Pulp exposure during caries removal will be recorded by the clinician in the CRF at the time of intervention. If soft tissue within the tooth is exposed this will be detected visually by bleeding and or a pink or red spot.

Progression of caries will be clinically and radiographically assessed by the clinician at each visit as per national guidelines. An independent blinded assessor will also evaluate the radiolucent area on radiographs taken between baseline and follow-up.

Tooth restoration failure and re-restoration will include the reason and subsequent treatment and will be collected at routine visits in a similar fashion to the primary outcome.

Patient-reported outcomes: will be recorded pre-treatment at or before the baseline visit and on an annual postal or online follow-up questionnaire until 3-years post-randomisation (except when indicated otherwise). This is to allow for data analysis on all collected data before to the end of the study funding. To help boost questionnaire response rates, SCRIPT practice staff will also give out a copy of the questionnaire to participants attending for dental check-up or treatment. The questionnaire will contain the same instruments as listed below, but will be branded as a clinic questionnaire. Participants can hand the completed questionnaire back to the practice team for return to the trial office, or can send it directly back to the study office in a prepaid envelope.

Dental pain and need for dental pain relief will be recorded on the annual patient questionnaire. Dental pain will be measured using a Numerical Pain Rating Scale (NPRS)[25].

Health status will be assessed using the generic EQ-5D-5L, consisting of five dimensions of Health Related Quality of Life (HRQoL).

Oral Health Related Quality of Life will be assessed using the Oral Health Impact Profile 14 (OHIP-14). OHIP-14 is the most commonly used validated oral HRQoL measure and has been used successfully in previous HTA trials[26].

Oral Health behaviours will be assessed at baseline and 3-years post-randomisation using questions about type of toothbrush, brushing twice a day for 2 minutes, frequency of interdental cleaning and behaviour after bursching.

Patient satisfaction: based on the NHS England commissioning of dental services guidelines[27] question of patient satisfaction with NHS dentistry we will explore patient satisfaction with their SCRIPT intervention on the annual questionnaire.

Economic outcomes: will include NHS and patient perspective costs, general population preferences, willingness to pay, incremental net benefits, and incremental cost per QALY. Outcomes measured over trial follow-up and modelled over a life time horizon.

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 selective and full caries removal, together with associated patient relevant outcomes. The DCE will be used to predict intervention uptake.

Process evaluation: will be conducted alongside the outcomes evaluation to include identification of possible facilitators and barriers to implementation.

Table 3: Study measures at each time point.

	Screening	Baseline (initial treatment visit)	At time of intervention/ Dental Visits	Annual Questionnaire	Up to 36 months	Other
Assessment for eligibility	○					
Informed Consent*		o				
Socio-demographic* characteristics & eligibility for free treatment		○				
Clinical Status (DMFT)		○				
Sustained Tooth Vitality			○		○	○
Pulp exposure during caries removal			○			
Caries progression			○		○	○
Dental Pain (NPRS) and need for dental pain relief*		•	•	•	•	
EQ-5D-5L*		•	•	•	•	
OHIP-14*		•	•	•	•	
Patient satisfaction			•	•	•	
Oral Health Behaviours*		•	•		•	
NHS perspective primary dental care resource use and cost			o			∇
NHS perspective use of other NHS services (GP, A&E etc).			o	•	•	
Patient perspective unit costs of time and travel						•
Patient perspective costs (private care, NHS co-charges etc).				•	•	∇
General population preferences						⊕
Willingness to pay						⊕

*according to participant preference these may be collected online prior to treatment visit
Legend:

- ○ Dental Practice-CRF
- • Questionnaire
- ∇ Data linkage to routine administrative datasets, ongoing over trial duration.
- ⊕ General population DCE, administered once.

Collection of data for data linkage and follow-up validation

National routine data collected for reimbursement of dental treatment provided will be used to inform the trial analyses. These data have been accessed successfully and used in several clinical trials. SCRIPT is the first opportunity to evaluate the possible added value of tooth-specific routine data in clinical dental research.

Tooth-level data in this study provides a unique opportunity to test, utilise and validate the use of routine data, from practices in Scotland and explore the potential for collection of data through BUPA, during a trial and assess its use over a long term follow-up period. SCRIPT trial clinical outcomes data will be linked in Scotland to treatment data held in the MIDAS. MIDAS which is held by Public Health Scotland (PHS) contains tooth-level treatment data for all patients treated by a primary care NHS dental provider working in Scotland. We will be able to monitor tooth-level treatment provided to SCRIPT participants for the duration of the trial and beyond. In England, while there is not a national database of tooth-level data, the inclusion of BUPA practices will allow exploration of collection of similar data through BUPA practitioners' IT systems. Within SCRIPT, these data will be evaluated regarding their validity for assessing clinical outcomes and economic modelling. In Scotland, MIDAS may help minimise loss to follow-up by providing a greater coverage than the study CRFs (e.g. if patients change clinician or go to a different clinician for out of hours treatment). In addition, estimates of its potential to monitor treatment on a specific tooth provided by any NHS dental provider working in Scotland or BUPA corporates will be assessed. Also, tooth-level data provide an unparalleled opportunity to accurately measure the costs of treatment and provide validation of long-term modelled treatment events beyond the trial follow-up period. We will undertake a validation analysis comparing (primary outcome) CRF data with data linkage follow-up data, which will also provide the opportunity for secondary and economic outcome data analysis if the data are valid.

Remaining resource use data will be collected on the annual questionnaires. This will include the use of other NHS healthcare services (e.g. GP visits and accident and emergency attendance) directly related to dental problems as well as data on indirect costs (e.g. time and travel costs, time off work, privately purchased care, self-purchased dental care products, including over the counter pain medications). The potential to gather other healthcare resource use through routinely collected data e.g. national Scottish Morbidity Records and national prescribing data sets will be explored.

7.2 SOURCE DATA

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, dental records (from which dental history may be summarised into the CRF) and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). In this study all clinical data are routinely collected in dental notes and other relevant documents and therefore the CRF will not be the source documents.

Participant completed questionnaires will be source data.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by the unique study number, not by name.

7.3 PROCESS EVALUATION

A mixed-method process evaluation will complement the outcome evaluation and examine implementation, mechanisms of impact and context as per MRC guidance[28]:

Implementation: the process through which the intervention (SCR or CCR) is delivered in dental practices, what is delivered in different practices and by whom, the fidelity and adaptation of the protocol and the resources used.

Mechanisms of impact: how the intervention is received by patients (acceptability) and how clinician/patient interactions trigger change in approaches to caries removal and placement of restorations and any unintended effects.

Context: through examining how external factors including dental contracts and the use of skill mix influence the delivery of the intervention and its outcomes. The process evaluation will include the self-report questionnaires as described above, analysis of trial outcomes data (including CRFs) and qualitative interviews with patients, dental professionals and other stakeholders such as managers of corporate bodies and dental service commissioners.

Process evaluation - qualitative interviews – SCRIPT participants

A sample of SCRIPT participants will be interviewed to explore their experiences of the intervention. A purposive sample will be used to ensure a range of participants in terms of age, patterns of dental attendance and tooth vitality or not. Potential participants for interview will be identified by the research team and they will be sent a letter of invitation along with a participant information sheet about the interview. Those who are willing to take part in the interview will return an expression of interest form to the research team. If they expressed an interest in being interviewed they will then be contacted by the researcher to arrange a suitable time and location to hold the interview. Before the start of each interview the researcher will obtain informed consent. Recruitment will continue until no new themes emerge. Previous similar studies have involved 10-15 patients in qualitative interviews[29]. The interviews will be guided by the concept of patient acceptability using a topic guide developed by the research team. The interviews will be audio-recorded and transcribed verbatim by a professional transcription service who will be approved as vendors by the Sponsor. The data will be analysed using framework analysis as it provides a pragmatic approach which produces results that can be easily incorporated into mixed-method studies, process evaluations and RCTs[30-32] (see details below).

Process evaluation - qualitative interviews – dental stakeholders
A sample of dental stakeholders will be interviewed during the set-up phase to explore their views about the usual care they provide and how they envisage delivering the intervention, and during the trial to explore their experiences of delivering the intervention within their own setting. Individual stakeholders may take part in one or two interviews, and may be interviewed at both time points to consider experiences of the trial in relation to expectations. Dental stakeholders will be purposively sampled based on role, geographical location, the types of dental contract they are working under, previous experience of differing restorative techniques and, for interviews carried out once sites have opened, their levels of engagement with the trial. Potential stakeholder participants will be selected, with dental professionals selected from the list of all practices involved in SCRIPT. The sample will include those who had recorded instances of having deviated from the clinical protocol for a variety of reasons, as these cases are of particular interest. Recruitment will continue until no new themes emerge. Previous similar studies have involved 25-30 stakeholders in qualitative interviews[33]. Potential participants for interview will be identified by the research team and they will be sent a letter of invitation along with a participant information sheet about the interviews. Before the start of each stakeholder's first and any subsequent interview the researcher will obtain and record informed consent using appropriate method, e.g. verbal, written, digital.

The interviews will be guided by the theoretical domains framework (TDF)[34] which has been used previously in implementation research to understand the motivations, cognitions and behaviours of dental professionals when implementing evidence-based practice[33, 35]. A topic guide based on the TDF has been developed by the research team. The interviews will be audio-recorded and transcribed verbatim by a professional transcription service who will be approved as vendors by the Sponsor. Framework analysis based on the TDF will be used.

The analysis 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 from grant-holders. 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 implementation and delivery of the intervention.

The process evaluation is being coordinated by grant-holders based at the University of Sheffield.

7.4 STUDY WITHIN A TRIAL (SWAT)

Poor retention of participants recruited to clinical trials is a known problem which can reduce statistical power, bias estimates of intervention effects and reduce the credibility of trial results[36]. SCRiPT will investigate whether giving participants a welcome letter on entry to the trial improves questionnaire response rates and retention across the trial's follow-up. The letter will welcome participants to the trial, reiterate the participant journey (summarising information provided in the patient information leaflet), identify the location of the participant's study tooth and list the expectations for participation i.e. the need to return the trial questionnaires. Allocation to receive or not receive the letter will be randomised following recruitment into the trial by the trial office and 50% of participants issued the letter within 2 months of consent to participate.

7.5 METHODS TO PROTECT AGAINST OTHER SOURCES OF BIAS

Monitoring fidelity with the clinical protocol is essential to exclude merger of the clinical techniques and consistency of technology used when more than one tooth has a deep carious lesion. We will implement the following strategies to assess compliance:

- In addition to using the **3D computer generated teeth** to clinically train clinicians, they will also be used during the phase of patient participant recruitment to monitor knowledge and skill. Clinicians will be asked after every third patient to cut both a SCR and CCR cavity in two sample teeth and return these to the research office. These teeth will be examined by a trial clinician to check for adherence to protocol. If merger of SCR and CCR is observed a second expert clinician will also examine the teeth for compliance with SCR and CCR and additional training and reinforcement of protocol will be provided. If necessary, a further two 3D printed teeth will be prepared and re-examined by the trial expert clinician. A sample of these teeth will be sectioned and examined by a clinical expert to monitor compliance. The sectioned teeth will also be used to enhance feedback to dentists where necessary.
- The **CRF will include an assessment of colour, hardness and consistency** to monitor whether SCR or CCR has been performed according to protocol. Coloured check boxes on the CRF will be used, to assess the colour of residual carious dentine after treatment. The lighter shade would be consistent with CCR, a darker shade with SCR. The hardness of the cavity will be assessed with a dental explorer/spoon excavator. Soft would indicate SCR and hard would indicate CCR. The consistency would be assessed with dental explorer and if moist after probing this would be consistent with SCR, if dry after probing, CCR. The CRFs will be assessed every 3 months to monitor fidelity and feedback will be provided if evidence of merger is observed.
- **Baseline and follow-up bitewing radiographs** will be assessed by two researchers masked to treatment group, to confirm the extent of initial caries and following the restoration the presence of caries. Where disagreement between researchers exists case discussion will take place and consensus agreed, this will then be compared with allocation. Feedback is not provided to dentists from this aspect of clinical monitoring. This is because (i) radiographs are 2-dimensional and some leeway is needed as decay might not be visible on all angles and (ii) some dentists may be less aggressive in their caries removal (and we have not recommended to remove caries if the pulp could potentially be exposed). Digital systems will aid the timely transfer of images however for those practices without digital systems either double film should be used or another copy provided so a copy can be sent for monitoring. Follow up x-rays will be taken at intervals judged appropriate by the clinicians therefore assessment will usually be 6-12 months after treatment.. At 2- and 3-years clinicians will record on CRFs whether there has been progression of caries. The CRF will record how this was determined and if x-ray is selected as a determining factor this will be reviewed by the independent assessors, but for the purposes of the analysis if there is disagreement then the categorisation by the clinician will be paramount as they have more information having looked in the participant's mouth.

7.6 DATA PROCESSING

Staff in the Trial Office will ensure the data is as complete and accurate as possible. A data monitoring plan will be developed and implemented by the trial office team.

7.7 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP53 Data Management Systems in Clinical Research.

A study specific bespoke database will be established and maintained by CHaRT. The access to the database is password controlled with personal access rights defined by the trial manager. The structure and content of the database will be individualised based on the protocol, the study outcome questionnaires and CRF. Report functions for continuous monitoring of recruitment, randomisation and follow-up will also be incorporated. The study database will be validated and will contain a full audit trail of data changes. The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be Professor Craig Ramsay.

The CI may delegate CRF completion but principal investigators at sites are responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial team.

Database lock will be conducted in compliance with CHaRT's standard operating procedures.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

The sample size calculation is event-based. We aim to detect an absolute improvement in sustained tooth vitality at three years of 12% from 80% (CCR) to 92% (SCR). The control rate of 80% is based upon the existing evidence base, clinical experience and confirmed by Scottish tooth-level routine data. As described in section 2.1 above, the current evidence base gives rates of pulpal exposure that are higher than those seen in UK NHS and therefore our rate of sustained tooth vitality will be higher than observed in those studies. The Bjørndal 2017 paper[14] presented a tooth vitality rate of approximately 80% at 3 years for two-step selective restoration in lesions that were deeper than those in this trial. The two-step procedure is more similar to a CCR than the SCR in our trial. The Scottish tooth specific data demonstrated that of 459,648 teeth that required a three surface restoration in 2013, 6.6% had received further endodontic treatment or were extracted at 3 years follow-up. These teeth however, could be at any level of pulpal dentine involvement and it is not possible to identify the level of involvement in the routine data. Therefore, as we are interested in only teeth with involvement in a pulpal third of dentine, we have estimated that the number of events may be three times larger. There is little empirical evidence to inform the expected size of an important effect. A target difference of 12% was judged clinically important and plausible by both dentists and our PPIE partners. The target difference of 12% was also informed by the difference observed in the Bjørndal 2017 paper[14] which was 13.7% at 5 years. However, as this is a patient RCT there are concerns around contamination (participants receive the intervention that they were not randomly allocated to). We conservatively have allowed for up to 25% contamination and therefore the sample size for SCRIPT aims to detect an absolute improvement of 9%; from 83% to 92% at three years. Recruitment of 623 participants (71 events) will detect a hazard ratio of 0.45 between experimental and control strategies and provide, using the log-rank test, assuming an exponential failure rate, 90% power at a 2-sided 5% significance level. The calculation also assumes 17 months of recruitment, a minimum of 33 months of follow-up and a 30% follow-up attrition at the end of year three. Recruitment is assumed to be staggered and builds in seasonal variation. We used the Stata package ARTSURV for calculations.

Update to sample size calculation (2023)
The original sample size of 623 was reviewed and revised to a minimum of 369 with the agreement of study oversight committees, sponsor and funder. One of the key assumptions within the original sample size was the proportion of people estimated to receive the non-allocated intervention (i.e. the proportion of contamination). As described in the original sample size above, the important difference to be detected by the trial is 12%. We had originally anticipated that the important difference of 12% would be "diluted" by 25% contamination and so assumed a smaller target difference of 9% in our sample size.

The Data Monitoring Committee, Trial Steering Committee and trial team reviewed the proportion of contamination using blinded data from SCRiPT. Of the 215 randomised participants that had received any trial intervention to that date, the rate of contamination was 2.3% (5/215). Conservatively assuming a contamination effect of 5%, the impact of contamination on the important difference of 12% is smaller than originally anticipated and the new target difference to calculate the sample size is 11.4% instead of 9%. The revised calculation and recruitment timelines assume 31 months of recruitment, a median of 34 months of follow-up with a minimum of 20 months follow-up, and 30% attrition. Recruiting 369 participants (41 events) will result in 80% power to detect a hazard ratio of 0.387. All remaining assumptions were kept the same as the original sample size. We used the Stata package ARTSURV for calculations.

8.2 PROPOSED ANALYSES

Demographic and baseline characteristics will be summarised and displayed in tables for all randomised patient participants using appropriate summary statistics. All analyses will initially be performed on an intention-to-treat basis, although we will also use causal methods for the analysis of the primary outcome to estimate efficacy in the presence of cross-over between treatment arms. All treatment effects will be presented with confidence intervals. Analysis will be fully specified in a Statistical Analysis Plan.

8.2.1 Primary outcome

The primary endpoint, sustained vitality, will be analysed within a time-to-event framework using a Cox proportional hazards model, adjusted for minimisation covariates and a random effect for clinician included. The treatment effect will be summarised by the hazard ratio with a 95% confidence interval. The estimated survivor function will be graphed.

8.2.2 Secondary outcomes

Secondary clinical time-to-event outcomes (progression of caries; tooth restoration failure and re-restoration) will be analysed in a similar manner to the primary outcome. Pulp exposure will be analysed using logistic regression adjusted for minimisation covariates and a random effect for clinician included. Secondary outcomes reported by participants will be analysed using mixed effects generalised linear models (using the appropriate link function for the outcome distribution) for repeated measures. Models will make use of data available at all time points, adjusted for minimisation covariates, fixed effects for treatment and (nominal) time points, and random effects for participant and clinician. The primary time point of interest will be 3 years post-randomisation. Treatment effects will be estimated using a treatment-by-time interaction and presented with 95% confidence intervals.

8.2.3 Planned subgroup analyses

Subgroup analyses on the primary outcome will explore the possible modification of treatment effect by age and number of lesions. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses.

8.2.4 Proposed frequency of analyses

From the internal pilot phase we will report estimates of recruitment rates and potential participant availability, together with appropriate confidence intervals. There are no planned interim analyses of the primary outcome; one final analysis will occur at the end of follow-up.

8.3 MISSING DATA

We will use strategies with proven effectiveness in improving retention to minimise missing data[37]. For participants who do not return or are censored early in the trial, dental practices will be contacted to find out potential reasons for missing data if they are available.

Participants with no event will be censored at their last visit with sustained tooth vitality. We anticipate that a small proportion of participants will not return at all, and a further proportion will be censored early in the trial because they do not come back to their clinician. We will consider how robust the findings are to these missing data using multiple imputation approaches under an assumption of missing at random, and using pattern mixture models. In participants with more than one eligible tooth, we will repeat our primary analysis with a clustering effect for participant.

8.4 TRANSFER OF DATA

Data transfer will adhere to the processes detailed in the CHaRT Standard Operating Procedure book. Briefly, electronic data transferred will be anonymised if possible and the data only identified by a unique study number. If this is not practical (e.g. for data linkage to such institutions as Information Services Division) then the data should be encrypted and password protected. The transfer may be made by encrypted email, or file transfer by ftp (File Transfer Protocol), over a secure site with appropriate security applied. However, sometimes it may be necessary to transfer files on CD or USB stick. In such cases, a robust system logging the receipt of sent items must be in place either for a CD coming into the centre or leaving the centre – for example, by registered mail or courier, requiring signature on delivery. As with electronic data, the data on the CD/USB stick should be encrypted and password protected using an acceptable standard of encryption currently available (at least 256-bit encryption).

Data transferred from CHaRT to external parties will be subject to approval by the Project Management Group using a data request form.

9 ECONOMIC EVALUATION

A full economic evaluation will be conducted. This will include a trial-based analysis at three years 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 over a modelled life-time horizon. 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) and cost per QALY will also be conducted as a secondary economic analysis to comply with NICE guidelines for technology appraisal.

9.1 ESTIMATION OF COSTS

Routinely collected dental claims data will be used to assess the costs to the NHS, and co-charges to patients of NHS provided dental treatments. Routine datasets will be supplemented with data collected using CRFs in the dental practice at each visit. Remaining resource use data, NHS and patient perspective costs directly related to dental problems will be collected using patient questionnaires. NHS costs of providing SCR and CCR will be based on the appropriate NHS contract-based payments to clinicians in the respective UK regions for the base case analysis. Contract payments detail the cost burden to the NHS but may not capture the full opportunity cost of time spent and materials used to deliver the interventions. Therefore, a micro-costing approach will also be used as a secondary analysis. Resource use data for the intervention micro-costing will include staff resource use and time, and consumables with information collected in a detailed CRF at the point of intervention delivery. Patient perspective costs will include patient co-charges for NHS treatments, time and travel costs, time-off work, privately purchased care and self-purchased dental care products, including over the counter pain medications. The participant time and travel cost questionnaire will be sent to all recruited trial participants to obtain unit costs for patient incurred time and travel. It is necessary to send the questionnaire to all participants. The sample reflects the minimum number of respondents contributing complete data that is required to enable a multi-variable regression to estimate costs according to a range of predictor characteristics of the sample. The minimum sample size is calculated from the formula N>= 50 + 8(k),[38] where k is the number of independent categories of the model assuming linear additive effects and no interactions. For k=15 explanatory variables in the model, the minimum number of fully complete responses to the questionnaire is N>= 50+ 8(15) >= 170. Assuming a questionnaire non-response rate of 30% and a further item non-response rate that would preclude running the model of 30% of returned questionnaires (as per the IQuaD study), the minimum number of questionnaires that need to be sent to obtain the required sample is N = 347 (170/0.7/0.7). The questionnaire will therefore be sent to all trial participants, once during the study. To maximise response rates to meet the sample size target, a postal reminder will be sent; if the participant does not respond, we will attempt to collect the data by telephone. The information collected will also be used to validate an external prediction model of time and travel costs that can be used in future research. Incremental NHS and patient perspective costs for SCR vs CCR will be estimated using generalised linear models with appropriate distributions for cost data and adjustment for baseline covariates.

9.2 ESTIMATION OF BENEFITS

WTP for the CBA will be elicited from a Discrete Choice Experiment (DCE). The DCE will be conducted with a nationally representative sample of the UK general population, using online panel surveys. The DCE will explicitly value preferences for provision of SCR and CCR, together with a range of plausible outcomes from the trial (e.g. sustained tooth vitality, longer term risk of repeat treatments and tooth loss). The DCE will examine the trade-offs between the potential benefits and risks of different treatment strategies. A cost attribute will be included to enable calculation of WTP. The DCE will also be used to assess the acceptability of SCR and CCR and predict uptake according to patient characteristics (investigating issues of preference heterogeneity for treatment). The target sample size for the DCE (N=1,067) is calculated using Dillman, 2007[39], 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.

9.3 TRIAL BASED ECONOMIC EVALUATION

Costs and benefits will be combined to estimate incremental net benefit (WTP – costs) and incremental cost per QALY gained for SCR vs, CCR over the three year trial follow up period. Deterministic sensitivity analyses will be undertaken to test the impact of assumptions and analysis methods on results. Subgroup analysis will be conducted at the region level if data allow in order to explore the potential impact of different payment systems across the UK regions on results. Results will be plotted on the cost-benefit and cost-effectiveness planes to illustrate the impact of sampling uncertainty on results.

9.4 DECISION MODELLING

The trial results will be extrapolated over a life-time horizon using a de novo tooth-level Markov model. The model will be built as a cohort model, but we will retain the option to move to a more flexible micro-simulation model if appropriate. Results will be reported using the same net benefit framework as the within trial analysis. The final model structure and health state definition (e.g. loss of tooth vitality, restoration failure, caries progression, and tooth loss) will be developed in conjunction with dental and patient experts. Survival analysis methodology will be used to assess the time to transition between health states, with survival curves

fitted over an extended time frame (patient's life time) to extrapolate the time to event data from the trial. The survival analysis will be supplemented with data from cohort studies and literature reviews to complete population of model transition probabilities and relative effects as required. Cost data (NHS and patient perspective) for health states will be sourced from the trial data and routine data sources (ISD / BSA). Benefits in terms of WTP will be sourced directly from the DCE for specific health states (e.g. WTP to avoid loss of tooth vitality, restoration failure, caries progression or tooth loss), together with WTP tariffs from previously conducted DCE studies[40]. Sensitivity analyses will explore the impact of key assumptions on cost-effectiveness results. Gaps in the evidence base will be identified and their potential impact on efficiency (net benefit) explored. Results will be presented on the cost-benefit plane and cost-benefit acceptability curves used to illustrate the probability that SCR is associated with positive or negative incremental net benefit. As with the trial-based analysis, secondary analysis will report incremental cost per QALY gained. A value of information analysis will be undertaken to determine the need for future research to resolve any residual decision uncertainty and an expected value of partial perfect information (EVPPI) analysis will be used to prioritise future cost-effectiveness research objectives.

10 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 TRIAL OFFICE DUNDEE

The Trial Office based in the Dundee Dental School at the University of Dundee will provide day to day support for the clinical centres and sites. The trial office through the trial manager and other administrative positions will provide a hub for dissemination of administrative and clinical support activities for the trial. The Trial Manager, Trial Administrator and Trial Secretary at the Trial Office Dundee will take responsibility for the day to day collecting, collating, handling and entering data for the participant completed postal questionnaires, including organising all aspects of the questionnaires (mailing, tracking, and entering returned data using the study web-based data entry portal).

10.2 CLINICAL TRIALS UNIT IN ABERDEEN

All the activities undertaken by the trial office in Dundee will be supported by CHaRT, the Clinical Trials Unit at the University of Aberdeen. The programmer at CHaRT will create, maintain and update all applications programmes for the trial, including the randomisation application and all administrative and analysis databases. The trial statistician (CHaRT) will produce the statistical analysis plan and undertake statistical analysis of the trial. The health economist will be responsible for the health economic evaluation and will be supervised by co applicants Boyers and van Der Pol. 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 during the trial, appropriate training of standard operating procedures, and will assist with any external monitoring and auditing of the trial. The Trial Manager based in CHaRT (Aberdeen) will take responsibility for supporting the regulatory requirements and the day to day transaction of study activities. The Trial Office team will meet formally at least once a month during the trial to ensure smooth running and trouble-shooting.

10.3 LOCAL ORGANISATION IN SITES

At each of the clinical centres, the Principal Investigators (Ricketts, Deery & Banerjee), will be responsible for clinical training and liaison with local practices. The PI and research nurse(s) in each site are responsible for all aspects of local organisation including identifying potential recruits, consenting, completing and maintaining appropriate documentation. The site agreement documents the full list of responsibilities for sites. Appropriate members of the local team are knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable. A trial-specific delegation log is completed and maintained by each site, detailing the responsibilities of each member of staff working on the trial. The local team is also responsible for notifying any safety concerns to the Trial Office.

10.4 PROJECT MANAGEMENT GROUP

The trial will be co-ordinated by its Project Management Group (PMG). The co-chairs of this group will be the Co-Chief Investigators and will consist of grant holders, representatives from the Trial Office and CTU. The PMG will meet/teleconference at least monthly however in the set-up stages this may be more frequent. In addition, the PMG will also meet at the annual Trial Steering Committee meeting. This consists of the grant holders and representatives from the Trial Office. Observers are invited to attend at the discretion of the PMG. The PMG has the expertise to cover the clinical and methodological aspects of the research.

10.5 TRIAL STEERING COMMITTEE

The TSC will oversee the conduct and progress of the trial. The TSC membership will consist of an independent Chair, at least two other independent members, at least one Patient and Public Involvement (PPIE) representative and the CI. Other SCRIPT grant holders and key members of the Trial Office team (e.g. the Trial Manager) may attend TSC meetings. The CI and team will identify and invite potential independent members to join the committee. The NIHR HTA will be invited to nominate a representative to sit on the TSC. Observers, other members of the PMG or members of other professional bodies can attend at the invitation of the Chair. Minutes of the TSC will be maintained in the TMF.

10.6 DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) will oversee the safety of subjects in the trial and will be independent of the TSC and trial co-applicants. It will be comprised of independent members, and the trial statistician will contribute as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate. The DMC will meet to monitor accumulating trial 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 trial. It is anticipated that both TSC and DMC will meet at least annually. The DMC Charter documents the terms of reference of the DMC and the names and contact details and is filed in the TMF. CHaRT has adopted the DAMOCLES Charter for DMCs. Minutes of the DMC will be maintained in the TMF.

10.7 INSPECTION OF RECORDS

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.

11 GOOD CLINICAL PRACTICE

The CI, all PIs, trial co-ordinators, research clinicians and nurses, and trial personnel will have undertaken any required Good Clinical Practice training.

11.1 ETHICAL CONDUCT OF THE TRIAL

The trial will be conducted in accordance with the principles of good clinical practice (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 trial.

The North of Scotland Research Ethics Committee (REC) 2, HRA (Health Research Authority) approval and R&D approvals will be sought. The trial will be conducted according to the principles of GCP provided by Research Governance Guidelines. Annual progress reports, end of Trial declaration, and a final report will be submitted to the Sponsor and the North of Scotland REC within the timelines defined in the regulations.

The trial will run under the auspices of the Trial office in Dundee Dental School 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 Good Clinical Practice (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 Local 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.

11.2 CONFIDENTIALITY AND DATA PROTECTION

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 user names 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.

11.3 INSURANCE AND 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.

11.4 PEER REVIEW

The trial protocol will be reviewed by the Trial Steering Committee (section 10.5) on behalf of the funder (National Institute for Health Research Health Technology Assessment Programme) and by the Research Ethics Committee. The justification for the trial and the proposed trial 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.

11.5 PUBLIC AND PATIENT INVOLVEMENT

Patients and members of the public have been actively involved, or will be involved, the following aspects of the trial:

- Design of the research
- Management of the research

- Undertaking the research
- Analysis of results
- Dissemination of findings

Patients and the public will be involved throughout the SCRIPT study via three main pathways to ensure regular and meaningful PPI. This will be facilitated by the HSRU Patient and Public Involvement and Engagement (PPIE) co-ordinator. The PPIE co-ordinator works closely with HSRU Public Partnership Group who will advise and contribute a public perspective and support patients and the public and researchers.

1. Study management: The Project Management Group includes one public representative (a co-applicant) and the HSRU Patient and Public Involvement and Engagement (PPIE) Co-ordinator. This will include review of patient facing documents, considering the patient perspective and patient burden both before, during and after involvement in the study, study design, recruitment, analysis, dissemination.
2. Study oversight: The Independent study steering committee. The study steering committee will include two independent patients or members of the public.
3. Responsive - study advice: as required. There may be times during the project that additional patient or public perspectives should be considered, as recommended by the study management or oversight groups. The HSRU PPIE co-ordinator will facilitate additional PPI as required. This may include, consulting other existing networks such as the Aberdeen young people's network, HSRU Public Partnership Group, or facilitating additional patient perspectives if required.

A detailed PPI plan will be co-developed between PPI partners and PPIE Coordinator on the study team.

12 ADVERSE EVENTS

12.1 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

12.2 EXPECTED ADVERSE/SERIOUS EVENTS

SCRIPT involves procedures and treatment which are well established in current NHS clinical practice and use. In this trial, 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.

- failure of tooth vitality with associated signs or symptoms (e.g. pain, infection, swelling, periodontitis)
- further treatment required

As this reflects the routine care the trial is designed to measure.
In addition, all deaths (any cause) are also recorded on the SAE CRF. Events that are serious but are not related to caries treatment in the trial tooth will not be recorded as SAEs.

12.3 RECORDING AND REPORTING AES/SAES

We do not anticipate any related AEs/SAEs in this trial. In addition, events that are not related to caries treatment in the trial tooth will not be recorded. SCRIPT involves procedures and treatment which are well established in current NHS clinical practice and use. In this trial failure of tooth vitality with associated

signs or symptoms (e.g. pain, infection, swelling, periodontitis) and further treatment required are captured as primary or secondary outcomes from the time a participant has their initial trial tooth caries treatment until their last trial follow-up, rather than being captured through adverse event or serious adverse event reporting processes. This reflects the routine care the trial is designed to measure. Outcomes within the trial will be regularly summarised and reported to the Data Monitoring Committee in their regular reports.

Death (for any cause) will be recorded on the CRFs.

Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an SAE.

13 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

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.

14 TRIAL CONDUCT RESPONSIBILITIES

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.

14.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

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.

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.

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

14.2 TRIAL RECORD RETENTION

Clinical data is entered into the database by the designated team members working in each site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office are entered there. Staff in the Trial Office work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks further enhance the quality of the data.

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.

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-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.

14.3 END OF TRIAL

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial 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 trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report is also issued to the funders at the end of funding.

At the end of the trial dissemination events will be organised to report research finding to key stakeholders (e.g.- patients/national patient advocates, clinicians, NHS England commissioners, GDP providers participating practices/participants) to deliver impact across wide audience. The Universities participating in the trial will work with their local Press departments to assist with access to the media. Live streaming and on-demand post event viewing will be made available.

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared.

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.

15.2 PUBLICATION

The clinical trial report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the trial.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

The findings of the trial will be disseminated widely through professional, primary care, public and scientific routes. The results of the trial will be reported in high quality research outputs including the HTA Monograph, journal papers and conference presentations to dental, public health, policy and wider audiences. The results of the trial will be used to update Cochrane reviews and clinical guidelines as published by NICE, SIGN and Scottish Dental Clinical Effectiveness Programme and the online training resource will be made available to learning institutions across the UK. In addition it is hoped to produce a range of actionable knowledge tools to encourage implementation of the trial results. The cost effectiveness elements of SCRIPT and patient related outcomes will be of high importance to the NHS policy and decision makers, including the UK's four

Chief Dental Officers and as such this trial has the potential to impact decision making for the general dental community both nationally and internationally. To enable this research to be embedded as an output and impact on future decision making we will draw on the extensive networks of the research team who are well connected, respected and cover a vast number of professional fields and demonstrate our ability to actively participate in creating a Global Evidence Ecosystem for Oral Health as aspired to by the MAGIC Project[41]. Many of the research team members are part of the academic teaching community for both undergraduate and postgraduate programmes. Through formal and informal channels and established teaching community networks, we will actively encourage Dental Schools to embed the research findings and clinical implications into teaching.

The results of the trial will be communicated directly to all participating dental practices who will be invited to attend the SCRIPT conference to showcase the results and work done by the practitioners involved. We will speak at national conferences for GDP's such as the British Dental Association conference, meetings and conferences of the Faculty of General Dental Practitioners and local practitioner meetings. We will continue 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 trial. We will produce clinical summary papers for clinician targeted journals.

Final dissemination events will be organised to report research finding to key stakeholders (e.g.- patients/national patient advocates, clinicians, NHS England-commissioners, GDP providers participating practices/participants) to deliver impact across wide audience. The Universities participating in the study will work with their local Press departments to assist with access to the media. Live streaming and on-demand post event viewing will be made available.

16 REFERENCES

1. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global Burden of Untreated Caries: A Systematic Review and Metaregression. In: Journal of Dental Research. Los Angeles, CA; 2015: 650-8.
2. Bernabé E, Sheiham A. Extent of differences in dental caries in permanent teeth between childhood and adulthood in 26 countries. *International Dental Journal* 2014;**64**:241-5. https://doi.org/10.1111/idj.12113
3. Bernabé E, Sheiham A. Age, period and cohort trends in caries of permanent teeth in four developed countries. *American journal of public health* 2014;**104**:e115.
4. World Health Organisation, Oral Health Country / Area Profile Project (CAPP). In: Oral Health Database. Sweden: Malmo University; 2006.
5. Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C*, et al.* UK health performance: findings of the Global Burden of Disease Study 2010. *The Lancet* 2013;**381**:997-1020.
6. NHS Digital. *Adult Dental Health Survey 2009 - England Key Findings*. The Health and Social Care Information Centre; 2009. URL: https://files.digital.nhs.uk/publicationimport/pub01xxx/pub01086/adul-dent-heal-surv-summ-them-eng-2009-re11.pdf (accessed).
7. Schwendicke F, Frencken JE, Bjørndal L, Maltz M, Manton DJ, Ricketts D*, et al.* Managing Carious Lesions:Consensus Recommendations on Carious Tissue Removal. *Advances in Dental Research* 2016;**28**:58-67. https://doi.org/10.1177/0022034516639271
8. Innes NP, Frencken JE, Bjørndal L, Maltz M, Manton DJ, Ricketts D*, et al.* Managing Carious Lesions: Consensus Recommendations on Terminology. *Advances in dental research* 2016;**28**:49-57.
9. Primary Care Team NHS Digital. *NHS Dental Statistics for England, 2016-17, Annex 1, Table 5a*. NHS Digital; 2016).
10. NHS National Services Scotland. *Primary Care Dentistry in Scotland Annual Report*. 2014/15. URL: https://www.isdscotland.org/Health-Topics/Dental-Care/Publications/2016-11-01/2016-11-01-PrimaryCareDentistry-Report.pdf (accessed).
11. Scottish Dental Clinical Effectiveness Programme (SDCEP). *Restricting the Use of Dental Amalgam in Specific Patient Groups*: Scottish Dental Clinical Effectiveness Programme 2018.

12. Pitts NB, Chadwick B, Anderson T. Children's dental health survey 2013. *Health and Social Care Information Centre www hscic gov uk/catalogue/PUB17137/CDHS2013-Report2-Dental-Disease pdf (cited 15 Jun 2016)* 2015.
13. Schwendicke F, Dörfer CE, Paris S. Incomplete Caries Removal: A Systematic Review and Meta-analysis. *Journal of Dental Research* 2013;**92**:306-14.
14. Bjørndal L, Fransson H, Bruun G, Markvart M, Kjældgaard M, Näsman P*, et al.* Randomized Clinical Trials on Deep Carious Lesions: 5-Year Follow-up. *Journal of Dental Research* 2017;**96**:747-53.
15. Bjørndal L, Reit C, Bruun G, Markvart M, Kjældgaard M, Näsman P*, et al.* Treatment of deep caries lesions in adults: randomized clinical trials comparing stepwise vs. direct complete excavation, and direct pulp capping vs. partial pulpotomy. *European Journal of Oral Sciences* 2010;**118**:290-7.
16. Ricketts D, Lamont T, Innes NP, Kidd E, Clarkson JE. Operative caries management in adults and children. *Cochrane Database of Systematic Reviews* 2013;**Mar 28(3)**:CD003808.
17. Lula ECO, Monteiro-Neto V, Alves CMC, Ribeiro CCC. Microbiological Analysis after Complete or Partial Removal of Carious Dentin in Primary Teeth: A Randomized Clinical Trial. *Caries Research* 2009;**43**:354-8.
18. Phonghanyudh A, Phantumvanit P, Songpaisan Y, Petersen P. Clinical evaluation of three caries removal approaches in primary teeth: A randomised controlled trial. *Community dental health* 2012;**29**:173-8.
19. Magnusson BO, Sundell SO. Stepwise excavation of deep carious lesions in primary molars. *Journal of the International Association of Dentistry for Children* 1977;**8**:36-40.
20. Foley J, Evans D, Blackwell A. Partial caries removal and cariostatic materials in carious primary molar teeth: a randomised controlled clinical trial. *British dental journal* 2004;**197**:697.
21. Leksell E, Ridell K, Cvek M, Mejare I. Pulp exposure after stepwise versus direct complete excavation of deep carious lesions in young posterior permanent teeth. *Dental Traumatology* 1996;**12**:192-6.
22. Villat C, Attal J-P, Brulat N, Decup F, Doméjean S, Dursun E*, et al.* One-step partial or complete caries removal and bonding with antibacterial or traditional self-etch adhesives: study protocol for a randomized controlled trial. *Trials* 2016;**17**:404.
23. Gusi N, Olivares PR, Rajendram R. *The EQ-5D health-related quality of life questionnaire. Handbook of disease burdens and quality of life measures*. US: Springer; 2010:87-99.
24. *Selection Criteria for Dental Radiography*. 3rd edn. London: Faculty of General Dental Practice (UK); 2018.
25. *Outcome Measures*. The British Pain Society and Faculty of Pain Medicine of the Royal College of Anaesthetists; 2019. URL: https://www.britishpainsociety.org/static/uploads/resources/files/Outcome_Measures_January_2019.pdf (accessed).
26. Slade GD. Derivation and validation of a short-form oral health impact profile. *Community Dentistry and Oral Epidemiology* 1997;**25**:284-90.
27. England NHS. *Introductory Guide for Commissioning Dental Specialties. 2015*. URL: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/09/intro-guide-comms-dent-specl.pdf (accessed).
28. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W*, et al.* Process evaluation of complex interventions: Medical Research Council guidance. *bmj* 2015;**350**:h1258.
29. Porritt J, Rodd H, Morgan A, Williams C, Gupta E, Kirby J*, et al.* Development and Testing of a Cognitive Behavioral Therapy Resource for Children's Dental Anxiety. *JDR Clinical & Translational Research* 2017;**2**:23-37.
30. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC medical research methodology* 2013;**13**:117.
31. Marshman Z, Innes N, Deery C, Hall M, Speed C, Douglas G*, et al.* The management of dental caries in primary teeth - involving service providers and users in the design of a trial. *Trials* 2012;**13**:143.
32. Oakley A, Strange V, Bonell C, Allen E, Stephenson J, Ripple Study T. Process evaluation in randomised controlled trials of complex interventions. *British Medical Journal* 2006;**332 (7538)**:413-6.
33. Newlands R, Duncan E, Prior M, Elouafkaoui P, Elders A, Young L*, et al.* Barriers and facilitators of evidence-based management of patients with bacterial infections among general dental practitioners: a theory-informed interview study. *Implement Sci* 2016;**11**.
34. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implementation science : IS* 2012;**7**:37.
35. Schwendicke F, Foster Page LA, Smith LA, Fontana M, Thomson WM, Baker SR. To fill or not to fill: a qualitative cross-country study on dentists' decisions in managing non-cavitated proximal caries lesions. *Implementation science : IS* 2018;**13**:54.

36. Walsh M, Devereaux P, Sackett DL. Clinician trialist rounds: 28. When RCT participants are lost to follow-up. Part 1: Why even a few can matter. *Clinical Trials* 2015;**12**:537-9.
37. Goulao B, Duncan A, Floate R, Clarkson J, Ramsay C. Three behaviour change theory informed randomised studies within a trial to improve response rates to trial postal questionnaires. *Journal of Clinical Epidemiology* Submitted.
38. Green SB. How Many Subjects Does It Take To Do A Regression Analysis. *Multivariate Behavioral Research* 1991;**26**:499-510. https://doi.org/10.1207/s15327906mbr2603_7
39. Dillman DA. Mail and internet surveys: the tailored design method. Hoboken, NJ: John & Wiley Sons. In: Inc; 2007.
40. Clarkson JE, Ramsay CR, Averley P, Bonetti D, Boyers D, Campbell L*, et al.* IQuaD dental trial; improving the quality of dentistry: a multicentre randomised controlled trial comparing oral hygiene advice and periodontal instrumentation for the prevention and management of periodontal disease in dentate adults attending dental primary care. *BMC Oral Health* 2013;**13**:58.
41. *The Digital and Trustworthy Evidence Ecosystem: Personalised eHealth solutions to increase value and reduce waste in health care*. MAGIC Evidence Ecosystem Foundation; 2018. URL: http://magicproject.org/archive/the-evidence-ecosystem/ (accessed).