FiCTION Trial

Filling Children's Teeth: Indicated or Not?

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CONTENTS

TRIAL SUMMARY

FULL TITLE:	Filling Children's Teeth: Indicated or Not?
SHORT TITLE:	FiCTION Trial
PROTOCOL VERSION:	4.0
PROTOCOL DATE:	09/11/2015
CHIEF INVESTIGATOR:	Jan Clarkson
SPONSOR:	University of Dundee
FUNDER:	National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme. Project number: 07/44/03
RESEARCH QUESTION	"What is the clinical and cost effectiveness of filling dental caries in primary teeth compared with no treatment?" In addition to comparing the clinical and cost effectiveness of a conventional filling-based strategy with prevention alone, an intermediate treatment strategy based on the biological management of caries, will be included.
TRIAL OBJECTIVES:	The primary objectives are to compare these three treatment strategies, when applied over a period of three years to 3-7 year old children with caries in primary teeth, with respect to the clinical outcomes of incidence of pain and sepsis. The secondary objectives are to compare the three treatment strategies with respect to: • incidence of caries in primary and secondary teeth; • patient quality of life; • cost-effectiveness over the period of the study; • acceptability and associated experiences of participants and parents; and • dentists' preferences.
TRIAL DESIGN:	The FiCTION Trial is a multi-centre, three-arm parallel group, patient randomised trial.
TRIAL INTERVENTION:	Arm 1 - Conventional management of caries (local anaesthetic, removal of decay and placement of a filling), with best practice prevention Arm 2 - Biological management of caries (sealing in decay with crowns, partial caries removal and fissure sealants), with best practice prevention Arm 3 - Best practice prevention alone
OUTCOME ASSESSMENT:	Outcomes will be measured at baseline and at review for a period of up to three years. Data will be collected by the participants' dentists, through patient and parent completion of questionnaires and through blinded assessment of radiographs.

Primary Outcome	*Measurement*
Either pain or sepsis related to dental caries.	Episodes of dental pain (toothache) measured by patient/ parent reporting and by dentist direct questioning Signs of infection detected through dentist clinical examination

Secondary Outcomes	*Measurement*
Incidence of caries in primary and secondary teeth	Caries experience recorded using ICDAS via CRF
Patient quality of life	Patient and parent completed questionnaires
Cost-effectiveness of arm (treatment strategy)	Parent questionnaire and data collection on clinical activity via CRF, study specific estimates of unit costs
Acceptability of treatment strategy to participants and parents and their experiences	Patient and parent questionnaires; parental interviews/ focus groups/ child participatory activities
Dentists' management strategy preferences.	Dentist questionnaire via CRF

TRIAL SITES: Dental practices in Scotland, North East England/Cumbria, Sheffield/Leeds/Derbyshire/Manchester/Liverpool/Wales/ London.

STUDY POPULATION: Children aged 3 - 7 years of age with at least one primary molar tooth with decay into dentine.

PARTICIPANT TIMELINE: Children within the correct age range will be identified through the participating practices and a letter inviting them to take part, will be sent to them and their parents with their next check-up appointment. Eligible children may also be identified at a routine dental visit. Parents and children who express an interest will have the trial discussed with them, and consent/assent obtained. Following random allocation of the child to one of the three treatment strategies, GDPs will treatment plan and manage the child according to allocation. A record of all dental treatment will be kept and the parents and children will complete questionnaires. The children will be followed up for three years when all dental treatment carried out will be recorded, and the parents and children will answer questionnaires.

STUDY TIMESCALE:

Funding start date:	01/01/12
Study start date	06/09/12
Planned finish:	31/06/17
Planned reporting date:	31/12/17

PROTOCOL CONTACTS & PERSONNEL

Sponsor:
University of Dundee
Research & Innovation Services
University of Dundee
11 Perth Road
Dundee
DD1 4HN

Co-Chief Investigator:
Professor Jan Clarkson
Programme Director, Consultant in Paediatric Dentistry
Dundee Dental Hospital and School, Park Place
Dundee
DD1 4HR
Tel: 01382 420060 / 07772115361
e-mail: j.e.clarkson@cpse.dundee.ac.uk

Co-Chief Investigator:
Professor Gail Douglas
Professor and Honorary Consultant in Dental Public Health,
Leeds Dental Institute, Clarendon Way
Leeds
LS2 9LU
Tel: 0113 343 9214 / 07590010666
e-mail: g.v.a.douglas@leeds.ac.uk

Co-Chief Investigator:
Professor Nicola P T Innes
Dundee Dental Hospital and School, Park Place
Dundee
DD1 4HR
Tel: 01382 425760/ Fax: 01382 206321
e-mail: n.p.innes@dundee.ac.uk

Co-Chief Investigator:
Professor Anne Maguire
Clinical Professor of Preventive Dentistry
Centre for Oral Health Research, School of Dental Sciences
Newcastle University, Framlington Place
Newcastle upon Tyne
NE2 4BW
Tel: 0191 208 8564 Fax: 0191 208 5928
e-mail: anne.maguire@ncl.ac.uk

Statistician:

Ms Vicky Ryan
Institute of Health & Society
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne
NE2 4AX
Tel: 0191 208 3676 Fax: 0191 208 8901
e-mail: vicky.ryan@ncl.ac.uk

Health Economist:
Professor Luke Vale
Institute of Health & Society
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne
NE2 4AX
Tel: 0191 208 5590 Fax: 0191 208 6043
e-mail: luke.vale@ncl.ac.uk

Miss Tara Homer
Institute of Health and Society
Baddiley-Clark Building
Richardson Road
Newcastle upon Tyne
NE2 4AX
Tel: 0191 208 8457 Fax: 0191 208 6043
e-mail: tara.homer@ncl.ac.uk

Senior Trial Manager:
Mrs Claire Macdonald
Newcastle Clinical Trials Unit
1–4 Claremont Terrace
Newcastle University
Newcastle upon Tyne
NE2 4AE
Tel: 0191 208 3825 Fax: 0191 208 8901
e-mail: claire.macdonald@ncl.ac.uk

Trial Manager:
Mr Mark Palmer
Newcastle Clinical Trials Unit
1–4 Claremont Terrace
Newcastle University
Newcastle upon Tyne
NE2 4AE
Tel: 0191 208 8393 Fax: 0191 208 8901
e-mail: mark.palmer@ncl.ac.uk

Clinical Leads:

Scotland
Dr Nicola P T Innes
Dundee Dental Hospital and School
Park Place
Dundee
DD1 4HR
Tel: 01382 425760
Fax: 01382 206321
e-mail: n.p.innes@dundee.ac.uk

North East England/Cumbria:
Professor Anne Maguire
School of Dental Sciences
Newcastle University
Framlington Place
Newcastle upon Tyne
NE2 4BW
Telephone: 0191 222 8564
Fax: 0191 222 5928
e-mail: A.Maguire@ncl.ac.uk

Sheffield/Derbyshire:
Professor Christopher Deery
Department of Oral Health and Development
School of Clinical Dentistry
Claremont Crescent
University of Sheffield
S10 2TA
Tel: 0114 2717885
Fax: 0114 2717843
e-mail: c.deery@sheffield.ac.uk

Leeds:
Professor Monty Duggal
Consultant and Head of Paediatric Dentistry
Leeds Dental Institute
University of Leeds
Clarendon Way
Leeds
LS2 9LU
e-mail: M.S.Duggal@leeds.ac.uk

Cardiff:
Professor Barbara Chadwick
Professor and Honorary Consultant in Paediatric Dentistry
School of Dentistry
University of Cardiff
Cardiff
CF10 3XQ
e-mail: ChadwickBL@cardiff.ac.uk

London:
Professor Ferranti Wong
Professor of Paediatric Dentistry/Honorary Consultant
Institute of Dentistry
Queen Mary University of London
Mile End Road
London
E1 4NS
e-mail: f.s.l.wong@qmul.ac.uk

Manchester/Liverpool:
Ms Vidya Srinivasan
Consultant and Clinical Lead in Paediatric Dentistry, Central Manchester Foundation Trust
Department of Child Dental Health,
University Dental Hospital Manchester,
Higher Cambridge Street,
Manchester M15 6FH.
Tel: 0161 275 6614
Fax: 0161 306 1559
e-mail: vidya.srinivasan@cmft.nhs.uk

Data Monitoring and Ethics Committee:

Professor Helen Worthington
Professor of Evidence Based Care and Co-ordinating Editor of the Cochrane Oral Health Group.
School of Dentistry
University of Manchester
Higher Cambridge Street
Manchester
M15 6HF
Tel: 0161 232 4707
Fax: 0161 232 4700
e-mail: helen.worthington@man.ac.uk

Professor Gerry Humphris
Professor of Health Psychology
Bute Building
St Andrews University
St Andrews
Fife
KY16 9TS
Tel: 01334 463565
Fax: 01334 463482
e-mail: gmh4@st-and.ac.uk

Professor Marie-Therese Hosey
Professor of Paediatric Dentistry
Kings College London Dental Institute
Denmark Hill Campus
Bessemer Road
London
SE5 9RS
Tel: 02032994078
e-mail: M.T.Hosey@kcl.ac.uk

PROTOCOL SIGNATURE PAGE

Protocol Authorisation Signatories

Signature ……. Date…….
Professor Jan Clarkson, Chief Investigator

Signature ……. Date…….
Ms Vicky Ryan , Statistician

Signature ……. Date…….
Professor Luke Vale, Health Economist

Signature ……. Date…….
Mrs Claire Macdonald, Senior Trial Manager

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BSPD	British Society of Paediatric Dentistry
CI	Chief Investigator
CPD	Continuing Professional Development
CRF	Case Report Form
DMEC	Data Monitoring & Ethics Committee
FFS	Fee for service
FGDP	Faculty of General Dental Practice
GCP	Good Clinical Practice
GDP	General Dental Practitioner
HTA	Health Technology Assessment
ICDAS	International Caries Detection and Assessment System
MCDASf	Modified Child Dental Anxiety Scale
MREC	Main Research Ethics Committee
NCTU	Newcastle Clinical Trials Unit
NIHR	National Institute for Health Research
P-CPQ	Parental-Caregivers Perceptions Questionnaire
PCRN	Primary Care Research Network
PCT	Primary Care Trust
PI	Principal Investigator (at each site)
PPQ	Parents' Perception Questionnaire
QOL	Quality of Life
R&D	Research and Development
RCT	Randomised Control Trial
RGF	Research Governance Framework
SAE	Serious Adverse Event
SPCRN	Scottish Primary Care Research Network
SUSAR	Suspected Unexpected Serious Adverse reaction
TSC	Trial Steering Committee
UDA	Unit of Dental Activity
VAS	Visual Analogue Scale
VDP	Vocational Dental Practitioner

KEYWORDS

Dental caries, caries prevention, primary teeth, prevention, paediatric dentistry, restoration, fillings, RCT, primary care.

1 INTRODUCTION

1.1 BACKGROUND

The lack of evidence for the effective management of dental decay in children's primary teeth is causing considerable uncertainty for the dental profession and participants. In particular, the apparent failure of conventional dental fillings to prevent pain and sepsis for UK children in primary care (1) has prompted much debate. At the present time, teaching in UK dental schools is based on guidance from the British Society of Paediatric Dentistry (BSPD) which includes the recommendation that the optimum treatment of decay in primary teeth should be its removal, followed by the placement of a conventional filling to replace lost tooth tissue (2, 3). However, these recommendations are largely based on evidence for the effectiveness of fillings obtained from studies conducted in either a secondary care or specialist paediatric dental practice setting. While both the volume and quality of the research on which this guidance is based is limited, it is acknowledged that fillings provided in specialist clinical environments can be effective (4). It is the generalisability of this evidence to a primary care setting that is in question and, in particular, the barriers, e.g. time, to providing fillings of sufficient quality to prevent pain and sepsis.

In the UK, the majority of dental care for children is provided in primary care by general dental practitioners (GDPs). Three recent studies, conducted in general dental practice in the UK, have provoked the current debate of what is appropriate and effective dental care for children with decay in primary teeth. The first of these was a retrospective case note study, based on a group of 50 GDPs' patient records, which suggested that placing a filling, compared with leaving the tooth unfilled, did not improve the clinical outcome in terms of dental pain and sepsis (1). In fact, the likelihood of children with filled teeth experiencing dental pain or sepsis was similar to that reported for the second study of 481 children who attended two general dental practices with a practice policy of leaving asymptomatic carious primary teeth unrestored, focussing on a preventive strategy alone to manage them (5). The third, and most recent study, was a randomised controlled trial involving 18 GDPs and, arguably, it provides the most robust evidence. The results demonstrate the ineffectiveness of a conventional, surgical approach (that is drilling out decay and placing a filling) to treating decay in children in general dental practice. This trial showed a failure rate in terms of pain and sepsis, after two years, approaching that reported by the previous two studies for unrestored teeth (6).

Perhaps because of perceived ineffectiveness, the traditional "drill and fill" methods of managing decayed primary teeth are not popular with GDPs (7). Less than 10% of decayed teeth in 5 year-old children are currently filled (8). However, a recent Cochrane review (9) found that emerging biologically-orientated strategies for managing decay (sealing some of the decay within the tooth rather than drilling it all out) are effective. In addition, a "biological" method of managing primary teeth by sealing in the decay with preformed metal crowns (PMCs) has been found to be both effective at preventing pain and sepsis, and acceptable to children, parents and GDPs (6).

Currently GDPs in the UK are providing care for children under different funding systems for general dental services. Whilst the implication of the funding systems on the type and quality of care is unknown, there is universal agreement that guidance for the effective management of decay is needed. In Scotland, the capitation and fee per item of service system is in operation, and to assist healthcare workers and participants the Scottish Dental Clinical Effectiveness Programme is currently in the process of developing national guidance for the management of decay in children. In England and Wales, many Primary Care Trusts (PCTs) are now seeking to secure adherence to best practice guidance as part of their clinical governance responsibilities when commissioning dental primary care services. However, the lack of direct evidence relevant to the setting where the vast majority of child dental care is carried out, i.e. general dental practice, and the discrepancy between the evidence for

restorative management of decay in the primary and secondary care settings, complicate the refinement of the process of care for what is the most common disease of young children. There is a gulf between the management strategies for decayed primary teeth recommended by the BSPD (and taught in UK dental schools), and the treatment currently being provided by GDPs. As yet, there is insufficient evidence upon which to base a recommendation as to which of three possible management strategies: the conventional surgical approach (traditional fillings); the biological approach (including sealing-in caries to stop its progress); or prevention alone where no fillings are placed, is the most effective at managing dental decay in children treated in primary care. The implication of this research is likely to be a change in policy for service and education in the NHS and beyond.

1.2 RESEARCH QUESTION ADDRESSED BY THE TRIAL

This multi-centre trial will address the HTA's commissioning brief and the research question "What is the clinical and cost effectiveness of filling caries in primary teeth, compared to no treatment?" It will also compare the clinical cost-effectiveness of an intermediate treatment strategy based on the biological (sealing-in) management of caries with no treatment and with fillings.

1.3 AIM OF THE TRIAL

The aim of the FiCTION trial is to compare the relative clinical and cost-effectiveness of the following three treatment strategies:

Conventional management of decay, with best practice prevention
Conventional management is commonly known as the 'drill and fill' method. In this treatment the tooth is numbed with a dental injection, then mechanical removal of the decay is carried out using a rotary instrument (drill) and a filling is placed in the tooth. Best practice prevention is carried out in line with current guidelines.

Biological management of decay, with best practice prevention
In this treatment arm, the decay is sealed from the oral cavity by application of an adhesive filling material, or by covering with a metal crown. Decay may, on occasion, be partially removed prior to the tooth being sealed. Injections are rarely needed. Best practice prevention is carried out in line with current guidelines.

Best practice prevention alone
With good oral hygiene it is possible to slow down the rate of tooth decay (5) with the aim of reducing the chances of primary teeth causing pain before they are shed. For the best practice prevention alone arm, no drilling, filling or sealing of primary teeth will occur. Dentists and other members of the dental team will base treatment plans for participants on best practice preventive care for teeth and oral health. Fissure sealants to secondary teeth and fluoride varnish may be applied.

1.4 OBJECTIVES

The primary objectives of this study are to compare the incidence of pain and sepsis experienced when following three treatment strategies for the management of dental caries in primary teeth when these are applied over a period of up to three years in 3-7 year-old children with caries in primary teeth. The three treatment strategies are:

- conventional restorations with best practice prevention;
- biological management with best practice prevention and;
- best practice prevention alone.

The secondary objectives are to compare these three treatment strategies with respect to:

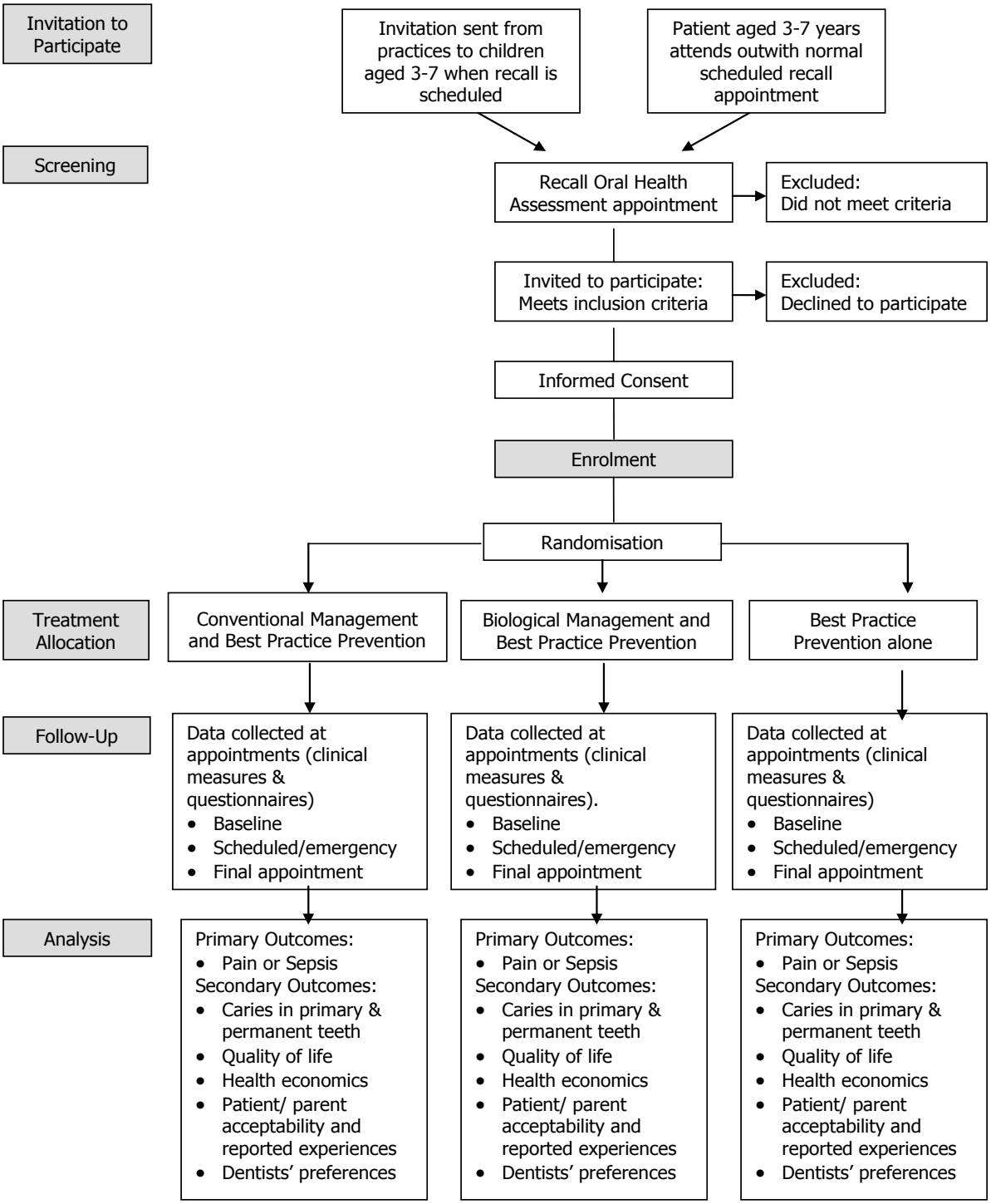
- incidence of caries in primary and secondary teeth;
- patient quality of life;
- cost-effectiveness over the period of the study;
- acceptability and associated experiences for participants and parents; and
- dentists' preferences.

1.5 STUDY DESIGN

The FiCTION Trial is a multi-centre, three-arm, parallel group, patient-randomised controlled trial. The trial will be set in Primary Care, reflecting the setting within which the vast majority of children's dentistry is carried out. An overview is shown in Figure 1.

The results of the FiCTION Pilot Rehearsal Trial and the parallel FiCTION Feasibility Study (Protocol ID HTA Project 07/44/03 NCTU:FS77044005), which were carried out between 01/01/10 and 31/10/11 and published in a Report to HTA – Pilot Trial and Feasibility Study, have informed minor refinements to the design and conduct of the trial.

Figure 1: Flow diagram of FiCTION Trial



2 PARTICIPANTS AND INTERVENTIONS

2.1 STUDY SETTING

General Dental Practitioners in primary care general dental practices will recruit 1,113 children, aged 3 – 7 years with dentinal caries (decay) in at least one primary tooth.

2.2 INTERVENTIONS

Three treatment strategies for managing caries in the primary dentition are being tested with each patient being allocated to one strategy and managed within that arm of the trial for three years.

Arm 1. Conventional management of decay, with best practice prevention
Conventional management is commonly known as the 'drill and fill' method. This is the traditional approach to managing caries that has been taught and practiced for many years. It is based on active management of caries by its complete removal. For dentinal caries in primary teeth this means teeth are numbed with local anaesthesia (a dental injection), then caries is mechanically removed using rotary instruments (drill) or by hand excavation (using hand tools) and a restoration (filling) is placed in the tooth to fill the cavity. If the dental pulp is exposed during caries removal or there are symptoms of pulpitis, a pulpotomy may be carried out. Retained roots, and teeth for which the crowns are unrestorable or the pulp chamber is open, are managed by extraction (removal) of the tooth following local anaesthesia.
Best practice prevention is carried out in line with current guidelines and as per Arm 3.

Arm 2. Biological management of decay, with best practice prevention
This approach to managing caries involves sealing it into the tooth, and separating it from the oral cavity by application of an adhesive filling material over the decay, or by covering with a metal crown. Decay may, on occasion, be partially removed prior to the tooth being sealed. Injections are rarely needed. Retained roots, and teeth for which the crowns are unrestorable, or dental nerves (pulps) exposed, are managed on a tooth by tooth risk analysis basis. Those with active caries (still progressing) or where the clinician decides the tooth is likely to give the patient pain or sepsis before it exfoliates (falls out) are managed by extraction following local anaesthesia.
Best practice prevention is carried out in line with current guidelines and as per Arm 3.

Arm 3. Best practice prevention alone
With good oral hygiene it is possible to slow down the rate of tooth decay. For the best practice prevention alone arm, no drilling, filling or sealing of primary teeth will occur. Dentists and other members of the dental team will base treatment plans for participants on best practice preventive care for teeth and oral health. This will involve four strands (all carried out according to current guidelines):

- Tooth brushing/ self-applied topical fluoride use;
- Dietary investigation, analysis and intervention;
- Fissure sealants for secondary teeth; and,
- Fluoride varnish applied to primary and secondary teeth.

2.3 PRACTICE ELIGIBILITY

Practices will be eligible for participation in the study if they:

- see and treat children aged 3-7 under NHS contracts
- see children with dental caries in primary teeth (around 1 child per week would be considered an appropriate frequency)
- have the infrastructure to support the study i.e. electronic patient management systems and internet access

2.4 RECRUITMENT OF PRACTICES

Practices will be recruited, from each of the five centres (Scotland, North East England/Cumbria, Sheffield/Leeds/Derbyshire/Manchester/Liverpool, London, and Wales) with –150 - 200 dentists to identify participants and enrol 1,113 participants. Selection of these practices will reflect the socio-demographic mix of the catchment communities. Practices where there has been an expression of interest in participating in the trial will be visited by the research team to assess their eligibility before being invited to take part.

Each practice will have a target of between 15 - 30 children to recruit over the recruitment period starting in October 2012.

General strategy

- The practices which participated in the Pilot Rehearsal Trial which took place in Scotland, Newcastle and Sheffield Clinical Centres will be contacted and the dentists invited to participate in the Main Trial.
- Practices which were contacted as part of the feasibility study (60 randomly selected practices in each of 4 areas and 33 in one area; n=273) and which responded by expressing an interest in participating in the main FiCTION Trial (n=70), will be contacted by letter and formally invited to participate in the Main Trial. Letters will be sent to the senior partner in each of these practices as well as the GDPs working in these practices (Total = 299 dentists).
- Practices which formed the overall sample for feasibility study but were NOT contacted as part of that study may be invited to express an interest in the FiCTION Trial (Total= 632 in the 5 areas).
- Any practice responding to general advertising in the dental press and expressing an interest in participating in the study will be considered in accordance with practice eligibility criteria and proximity to the Clinical Centres.

Local strategy

To allow for local factors which might influence recruitment, in addition to the general strategy for recruitment of practices, a local recruitment strategy will be developed by the Clinical Leads in liaison with the research networks in England and Wales and the SPCRN in Scotland. This will comprise email and postal mailing of FiCTION flyers to practices and practitioners by CLRNs and their equivalents in Wales and Scotland. Practices wishing to express an interest in the study will be asked to contact the Dundee FiCTION Trials Office. Expressions of interest will be followed up locally by the Clinical Leads with the support of the local primary care research networks. Local practice recruitment meetings will be held in the Clinical Centres to inform interested GDPs about the FiCTION Trial and answer any questions they may have.

2.5 RETENTION OF PRACTICES

The Trial Manager, Clinical Lead's secretaries and Clinical Researcher will actively maintain contact with all trial practitioners throughout the study. They will identify any practice retention or associated problems early, using the formally established communication strategy and informally through their availability to, and regular contact with, the practices, working closely with the practitioners to troubleshoot.

CPD for all members of each FiCTION practice dental team will be made available for attendance at any trial meetings.

Weekly email and telephone updates and regular newsletters will be issued during the trial.

A final report will be issued to all of the participating dentists.

Active support from the PCRNs, research networks and local research champions for recruitment and retention of practices will be sought.

2.6 TRAINING OF DENTISTS & PRACTICE STAFF

Good Clinical Practice/ Research Governance Framework Training

All members of the trial team and practice staff will have training in Good Clinical Practice in keeping with the role that they are asked to undertake on the study. Dental practices will be required to maintain an Investigator Site File that contains evidence of staff involved, their training and their delegated roles. Dentists will be named as Practice Leads following them satisfying the GCP/ RGF requirements.

In addition to this GCP training, practice staff directly involved with recruitment and consent will receive further training in taking informed consent in a paediatric setting.

Trial Specific Training

Each Clinical Centre will host a Practice Training Day to deliver clinical and trial process training to all enrolled dentists at a Practice Training Day. Dental team staff (dental therapists/ hygienists/ nurses and practice receptionists/ managers) will also have their training delivered, where possible, at the Practice Training Day. For dental team staff who cannot attend a Practice Training Day, training will be delivered as part of the Site Initiation Visit by the Trial Manager and Clinical Researcher.

Training will be provided for individual clinical procedures that dentists may be unfamiliar with. Although this will be tailored as far as possible for each group of dentists, from our experience with the Pilot Rehearsal Trial, this will include, but not be limited to, recording dental caries using the International Caries Detection and Assessment System (ICDAS), taking radiographs, the Hall Technique and conventional crown provision. Additional training materials have been developed for taking radiographs (included in the Clinical Protocol supplementary documentation) and for the Hall Technique (a DVD) that dentists will have available in their practice. Given the importance of the detection of dental infection/sepsis (as a primary outcome), although this is a standard part of a dental clinical examination, there will be training directed specifically at this.

Training will be given in the treatment planning of children appropriate to each arm of the trial. This will involve a didactic teaching session followed by practical treatment planning with cases and discussion with the local Clinical Lead and Chief Investigators.

2.7 TARGET SAMPLE SIZE

The original aim was to invite 18,717 children to attend for screening with an expected 12,166 (65%) of these actually attending and agreeing to be screened for the study.

It was expected that 1825 children (15% of those screened) will be eligible for the Trial. Of these it was anticipated that 1460 (80% of those eligible) will consent to be randomised, with 487 children allocated to each of the three study arms.

Allowing for a loss to follow up of 25% over three years it was anticipated that outcome data would be available for 365 children in each intervention arm.

At the planning stage, the proposed primary outcome was the proportion of children reporting either pain or sepsis during three years of follow up. Based on evidence from previous studies on similar populations with no fillings (1, 5), and conventional fillings and the Hall Technique (6) sepsis rates of 20%, 10% and 3% respectively were expected. Using the "sampsi" procedure (a sample size calculation based on a two-sample test of proportions assuming a normal approximation and incorporating a continuity correction) in Stata version 9, assuming a significance level of 2.5% (to allow for multiple testing involved in a three arm trial) the following was calculated as the required sample size:

- two groups of 334 children to detect a difference in rates between 10% and 20% with 90% power
- two groups of 334 children to detect a difference in rates between 3% and 10% with 90% power

The sample size was then increased by an inflation factor of 1.09 (giving 365 children per arm at end of follow up) to allow for adjustment of estimates of effect size taking into account variation between randomisation strata (dental practices).

However, a contract variation request was submitted to the HTA in August 2014 explaining that based on the recruitment trajectory at the time, with recruitment anticipated to continue until December 31st 2014 and follow-up until 30th June 2016, the study would only recruit 1113 children. This would correspond to an effective sample size (after allowing for loss to follow up and adjustment for strata) of three groups of 255 children with a mean length of follow-up of 24.6 months, which (assuming a linear incidence of pain or sepsis over the follow-up period) would result in only 55.6% power to detect a difference between the arms for the primary outcome; pain and/or infection, assuming a type 1 error rate of 2.5%.

Hence, three possible alternative 'Scenarios' were put forward by the FiCTION team to the HTA who approved Scenario 1, detailed below:

Extension to study in months		12
End of Recruitment		31.12.14
End of follow-up		30.06.17
End of trial		31.12.17
New Practices		No
Target recruitment		1113
Mean length of follow up in months		35.5
Power depending on whether adjustment for strata is necessary	No	82%
	Yes	77.4%

It was subsequently agreed that due to the already variable follow up that to maximise the chances of reaching the desired power, recruitment could continue until 31st June 2015 and that new sites could be added to facilitate this recruitment on the understanding that any costs this may incur were to be absorbed by the current budget.

2.8 CHILD PARTICIPANT INCLUSION CRITERIA

Child participants (3-7 years of age), male and female, who:

1. are willing to be dentally examined;
2. have at least one primary molar tooth with decay into dentine; and
3. are known regular attendees or, if new to the practice, considered likely to return for follow-up

2.9 CHILD PARTICIPANT EXCLUSION CRITERIA

1. participants who are accompanied by an adult who lacks the legal or mental capacity to give informed consent;
2. participants who, at the recruitment appointment, present with either pain or dental sepsis (as diagnosed by the GDP from patient history, examination, radiographs) associated with dental caries. These participants will not be enrolled into the study at this point, but after treatment may be reassessed for eligibility. *Discomfort associated with erupting teeth/exfoliating teeth, an incident of trauma or oral ulceration, is not an exclusion criterion*;
3. participants with a medical condition requiring special considerations with their dental management, e.g. cardiac defects, blood dyscrasias;
4. participants currently involved in any other research which may impact upon this study; and
5. participants in families who know they will be moving out of the catchment area for the dental practice during the 3 years following recruitment.

2.10 WITHDRAWAL CRITERIA

Participants have the right to withdraw from the trial at any time without having to give a reason. Practices should try to ascertain the reason for withdrawal and document this reason within the Withdrawal Form.

2.11 IDENTIFICATION AND RECRUITMENT OF PARTICIPANTS

The following strategy has been refined based on the results of the Pilot Study.

A sample of children between the ages of 3 and 7 years will be identified from participating dental practices. The screening process for identification of participants for the trial will be through routine dental examination ('check-ups'). Participants will be identified and invited to participate through two routes:

- The recruited FiCTION practices will carry out simple searches on their practice databases in order to identify potentially eligible children using a date of birth query.

  Potentially eligible children due for a recall appointment will be invited to participate by letter of invitation from the child's GDP. This letter, together with an information sheet for parents and an information sheet for the child, will be sent with their dental appointment card at least one week in advance of the scheduled recall appointment.

- Opportunistic recruitment of participants who present to recruited FiCTION practices and have caries into dentine in at least one primary tooth.

  Parents of children presenting opportunistically, and identified as being potentially eligible for participation, will be invited to participate. Unless they decline, parents will be given the invitation letter and the parent and child information sheets and time will be allowed (minimum of 24 hours) to consider participation in the trial before consent is sought.

Potential participants from both routes will have a routine screening examination to confirm eligibility. This screening will consist of standard dental recall clinical investigations (questioning regarding oral pain since last visit, current oral pain, clinical examination of the soft tissues and teeth, radiographs in line with national guidance) and standard dental recall medical checks. This will allow the identification of children with dental caries and will also allow children with current pain or sepsis and medically compromised children to be excluded from the study. The Patient Information Sheet includes the telephone numbers of the GDP and of the research team and parents will be encouraged to use them to discuss any questions at any stage of the study. Replacement copies of the Patient Information Sheets will be available from the practice.

At the post-screening recall/recruitment appointment, if there is evidence of caries, and absence of pain and sepsis, a FiCTION -trained dentist in the practice will discuss the trial with the parent and child, supplementing the trial information already received and will answer any questions they may have. If the parent and child are willing to participate, written informed consent will be obtained from the parent and oral or written assent will be obtained from the child, by the FiCTION-trained dentist prior to any study specific procedures being carried out. A short pictorial information sheet (script and pictures) will be available for practices to help in the assent process for younger children or children who struggle with reading. Once consent/assent has been obtained a child participant will have a detailed baseline dental examination carried out. For children where consent is not given for participation in the trial, the dentist will carry out the child's normal dental care.

For those children without evidence of caries into dentine, or where pain and/or sepsis are present the GDP will explain why it is not possible to take part in the FiCTION trial at that time. If a child is free of caries at the screening check, but then develops caries during the course of the trial period they may be invited to join the study if the recruitment phase is still active. Similarly, if on a subsequent visit a child with caries presents and no longer has the pain and/or sepsis evident at the initial screening, they may be invited to join the study.

Other dental team members of a FiCTION practice (Vocational Dental Practitioners (VDPs), Dental Therapists and Hygienists) may be invited to participate in the trial by a FiCTION-trained Dentist in the practice. VDPs will be able to assist recruitment by screening participants. However, all eligible children who agree to participate will see a FiCTION-trained Dentist, who is GCP trained and who has attended instruction in each of the three arms of the trial. The FiCTION-trained dentist will be responsible for consent processes and providing a treatment plan for the VDP, in-line with the participants' allocated arm. Alternatively, if all parties (including the patient) wish, the FiCTION-trained Dentist will carry out the child's treatment. VDPs, Dental Therapists and Hygienists will be able to carry out treatment plans prescribed by a FiCTION-trained Dentist (according to their GDC remit).

Once eligibility has been confirmed by the FiCTION-trained dentist and informed consent and assent given, participants will be given a subsequent treatment appointment, prior to which randomisation via the NCTU randomisation service will be carried out. Upon attending this subsequent appointment participants will be informed as to which treatment arm has been allocated to them, will have a detailed dental chart completed and will commence treatment

as per protocol. Participants will also be given a letter to give to their General Medical Practitioner, informing them of their involvement in the study.

Participants recruited at practices that have expressed interest in being involved in future studies (linked to FiCTION) will be given the opportunity to consent to provide their contact details to the FiCTION team. Parents will be invited to read the information sheet at their child's routine appointment and provide consent/ complete the contact details form.
Any future studies, for which contact with FiCTION participating children or their families is required, will be subject to full REC application.

A poster to highlight the FiCTION study will be available to practices to display.

2.12 PARTICIPANT RANDOMISATION

The target sample size to be recruited and randomised for the trial is 1,113 children who meet the eligibility criteria and agree to participate (see Section 10). The trial will comprise simple randomisation of participants into the three caries management strategies in a 1:1:1 ratio. Randomisation will be through the web-based, automated central randomisation facility at the Newcastle Clinical Trials Unit (NCTU) using variable length random permeated blocks to ensure concealment of allocation. The intention is that participants will be managed throughout their time in the study according to the randomisation arm to which they were allocated, i.e. any subsequent episode of caries will be managed in the same way (as per random allocation) as the initial episode. Any crossover that does occur because participants or parents transfer to another arm or opt to have treatment that is part of another arm will be monitored and recorded at annual study recalls.

The different treatments that will be applied in each arm mean that it is not possible to blind the parents, children, or dentists as to which arm the child is participating in.

2.13 RETENTION OF PARTICIPANTS

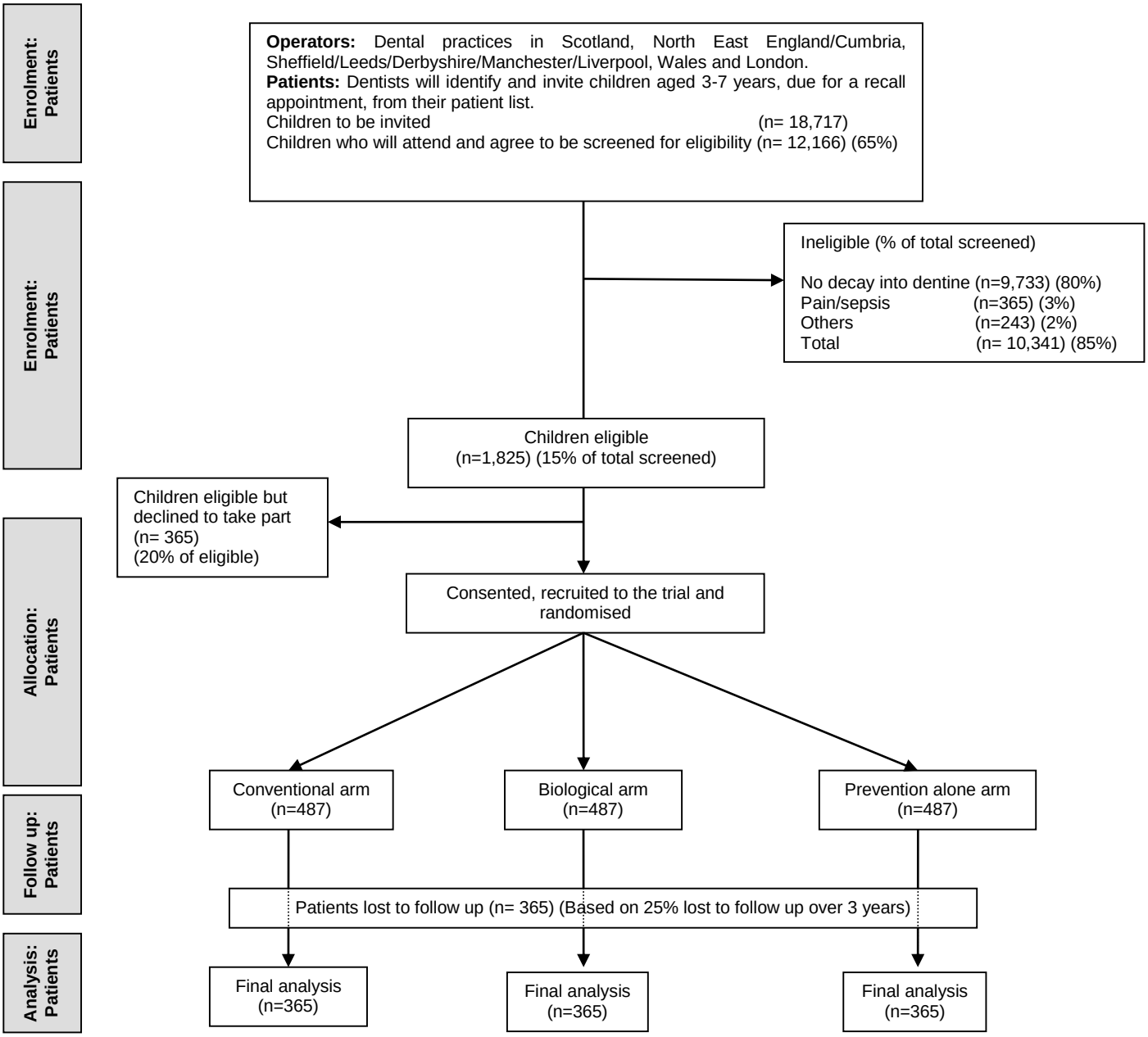
Upon enrolment, parents and participants will be given FiCTION Trial Membership Cards stating that they are part of the study and carrying details of their dentists and who to contact regarding the study should they move to a new dentists/ practice or need to seek out-of-hours or emergency dental care. This card also gives details of the FiCTION website which will provide material for the children to access for colouring-in and other activities as well as updated information on how the study is progressing and how to contact members of the study team. We are also distributing leaflets and posters for display in practice waiting rooms to convey our thanks to the FiCTION families for their participation, while enhancing the trial's prominence within practices, sending the children birthday cards via the practice as well as maintaining feedback from practices in order to guide development of suitable FiCTION branded merchandise promoting the study.

2.14 PARTICIPANT TIMELINE

Children within the correct age range will be identified through participating practices and a letter inviting them to take part will be sent with their next check-up appointment. Eligible children may also be identified at a routine dental visit. Parents and children who are interested will have the trial discussed with them, and consent obtained. Following random allocation of the child to one of the three treatment strategies, FiCTION-trained dentists will treatment plan, manage and follow up the child according to allocation. At the treatment appointments, the parents and children will complete questionnaires. Participants will be followed up for three years and data on all treatment provided over the study period will be collected annually at a FiCTION recall visit. If a participant fails to attend a scheduled or final

appointment the practice will post the appropriate time point questionnaire with covering letter and pre-paid envelope to the participant for completion (see 3.2 Data Management).

Figure 2: The projected flow of children through the study (based on the original sample size calculation)



3 DATA COLLECTION AND PROCESSING

3.1 PRIMARY OUTCOMES

Pain (toothache)
Assessments for pain will be made at each visit (treatment or recall) throughout the patient's participation in the trial. Pain resulting from toothache / other oral pains will be assessed using the CRF completed by dentists and the Dental Discomfort Questionnaire (DDQ8) and will be completed by the parents. The DDQ8 has been shown to be a valid and reliable measure of toothache in young children (in a sample with a mean age of 4 years) and may be abbreviated to just 8 items (DDQ8) (10). The DDQ8 is completed by parents and is therefore a proxy measure of discomfort through observations of the child's behaviour. In order to differentiate between pain originating from a decayed tooth and pain from other causes, the dentist will form a diagnosis based on patient/parent history and the clinical evidence available from examination, which will be recorded on the CRF. This outcome will be the number of children in each treatment arm experiencing toothache pain and the number of episodes of pain for each child in each arm during the follow-up period. This will be recorded using the CRF completed at the time of each treatment or review appointment.

Sepsis (dental infection)
Assessments for sepsis will be made at each visit (treatment or recall) throughout the patient's participation in the trial. The outcomes are clinical (from examination by the child's dentist) and radiographic signs (assessed by a dentist and an independent assessor). Clinical visual examinations for sepsis will be specifically undertaken at every dental visit by the GDPs, and recorded on the CRF. These examinations will be supplemented with independent examination of any bitewing radiographs that have been taken (in line with FGDP guidelines) to record radiographic signs of inter-radicular pathology. The clinical detection criteria for the positive recording of sepsis will be the presence of a swelling, dental abscess or draining sinus. Although GDPs will be familiar with the signs and symptoms of sepsis we will develop their FiCTION training to ensure it is reliably and reproducibly recorded.

Data for the primary outcomes of pain and/or sepsis will be recorded during or following appointment times when the participant attends for both scheduled appointments and unscheduled/emergency appointments.

3.2 SECONDARY OUTCOMES

Incidence of caries in primary and secondary teeth
Detailed measurements of caries experience will be recorded at baseline and final assessment by the GDPs using the CRF. The dentists will measure both early and more advanced stages of dental caries. The primary requirement for the examination is clean, dry teeth. All surfaces of all teeth will be examined and the status of each recorded in terms of caries and restorations. Bitewing radiographs, taken in line with FGDP guidelines (with blinded, independent assessment) will be used as an independent measure of dental caries. However, as frequency of bitewing radiographs is based on caries risk assessment, and as some children may move out of the high risk group during the course of the trial, the frequency of bitewing radiographs taken for some children may reduce over the period of the study.

Quality of Life
Oral health related quality of life will be measured at the beginning of the study and at the end of the study. The measurement of quality of life in children is complicated by the rapid changes seen as children grow (11, 12) including the development of children's levels of literacy and

understanding. For children under six years of age the use of simple child-completed scales or questionnaires completed by parents as proxies is the usual solution (13).

Parents will still be asked to complete a 16-item Parents' Perception Questionnaire (PPQ) (Murray Thomson personal communication. OHRQoL Symposium, BSODR, Sheffield, 2011). The full length version of this measure has been found to be reliable and valid for use in the UK (14). In addition, parents will be asked to evaluate their child's overall oral health-related quality of life by responding to two single item ratings worded:

"Would you say that the health of your teeth, lips, jaws and mouth is...?" with a 5-point response format ranging from 'Excellent' to 'Poor'

"How much does the condition of your teeth, lips, jaws or mouth affect your life overall?" with a response range from 'Not at all' to 'Very much'

These questions are routinely used with the PPQ (15), and have been included in several UK studies (16). These measures of Oral Health-related Quality of Life will be recorded at baseline and at the end of the study.

A child-centred qualitative approach with participatory activities will be undertaken towards the end of trial, to explore the children's experiences and the acceptability of the three caries management strategies to children (17). Separate ethics approval will be sought for this part of the study.

Economic

To allow a full understanding of cost-effectiveness and add value to the analysis, two different ways of measuring incremental costs will be compared; a time/material-based cost and the current cost to the NHS.

Time and material based cost: an appropriate fee structure and an understanding of the opportunity costs will be essential prior to implementation of any arm of the trial. It is known that fee structures influence practise. However, they do not necessarily represent the costs related to the dentist's time and materials and may result in perverse incentives. Furthermore, there is no specific fee for some of the procedures encompassed in the biological arm, despite different time and material costs. Consequently, a "procedure cost" using time in the surgery and materials used will be applied for the common operative interventions in the conventional with prevention, biological with prevention and prevention alone arms. Data on resource use will be collected via the CRF for each enrolled patient for every scheduled and unscheduled visit. This will include the number of dental visits, treatments undertaken and appointment duration. This data will be combined with a micro costing study based on data recorded from direct observation of a number of centres during the trial. The micro costing study will estimate the resources used to provide the interventions, e.g. equipment (disposable and reusable) consumables and staff mix. The costs of onward referral (for example, for hospital admission for extraction of painful teeth under general anaesthesia) will be obtained from existing data available within the NHS.

Current cost to the NHS: the payment systems in Scotland and England/Wales differ therefore the costs of clinical interventions to the NHS will be calculated using the standard fees from the fee-per-item arrangements in Scotland, and an agreed UDA value in England/Wales. The UDA information will be collected annually via a short survey sent to each participating practice. In the event that this information cannot be collected from practices we will ask the PCT to provide this information. FFS (fee for service) information will be based on nationally available data (Information Services Division Scotland). This costing strategy will allow actual NHS costs to be calculated whilst highlighting any variability in cost effectiveness resulting from the different payment systems.

Data on parental costs (time off work, child care costs and over-the-counter medications) will be collected using previously developed and tested questionnaires. This data will be collected via the Adult Scheduled and Unscheduled visit questionnaires administered every time a child visits the dentist.

Cost-effectiveness analysis: the relative cost-effectiveness of each arm will be assessed by considering both the cost per sepsis-free patient and cost per pain-free patient. The incremental cost per pain/sepsis episode will be calculated, with usual dental care (conventional (surgical) caries management) as the base case. Sensitivity analysis will be performed to test the robustness of the results to realistic variations in the levels of the underlying data. For details see section 4.2.3.

Acceptability of treatment strategies, and experiences of, participants and parents
To measure the acceptability of the treatment strategies experienced, dental anxiety of children will be assessed. The Modified Child Dental Anxiety Scale - faces (MCDASf) is a rating scale based on faces instead of the original numeric form. The reliability and validity of MCDASf has previously been evaluated for use in children in the UK (18). The MCDASf will be administered at baseline and every recall and treatment appointment to provide information on children's perceptions of each dental experience throughout the study.

At the start of each appointment the child will be given a faces-based Visual Analogue Scale (VAS) to report on their level of anxiety prior to arriving at the dentist's for their appointment. They will also be given a faces VAS following each treatment appointment to report on their level of anxiety during treatment.

Parents' assessment of their child's anxiety level prior to arrival at the dentist's for their appointment and following treatment will also be recorded using a VAS.

Given the difficulty in measuring children's attitudes towards treatment strategies, identified in the pilot rehearsal trial, the acceptability of the three treatment strategies will be explored using child-centred interviews which incorporate child participatory activities to allow children rather than adults to shape the data collection process (17).

Discomfort during dental treatment will be assessed using a Visual Analogue Scale (VAS – completed by the child). VASs are often used with children to assess self-reporting of such measures as fear or pain and can be used from a very young age with acceptable levels of reliability(13). At the end of each appointment the child will be given a faces VAS to report on their levels of pain in relation to that particular visit. In addition, parents will also be asked to report on their perceptions of their child's levels of pain regarding that particular visit to the dentist.

Dentists' preferences
Exploration of dentists' preferences between the 3 treatment strategies will be explored qualitatively through interviews/focus group using a method most convenient to study dentists. Topic guides will be derived from qualitative information collected during the FiCTION pilot rehearsal study.

Data management
To preserve confidentiality, all participants will be allocated a unique study identifier, which will be used on all data collection forms and questionnaires; names or addresses will not appear on completed questionnaires or case report forms. Only a limited number of members of the research team will be able to link this identifier to patient-identifiable details (name & address) which will be held on a password protected database. All study documentation will be held in secure offices, and the research team will operate to a signed code of confidentiality. Transmission of identifiable data between practices, coordinating centres, the NCTU and the University of Dundee (the study sponsor) will be by secure fax, registered post or carried by a study team member. A clinical data management software package compliant with FDA 21

CFR Part 11 requirements regarding electronic records and electronic signatures will be used for data entry and processing, allowing a full audit trail of any alterations made to the data post entry. Original questionnaires, case report forms and consent forms will be securely archived at the University of Dundee for 7 years following publication of the last paper or report from the study.

4 STATISTICS AND DATA ANALYSIS

4.1 PRIMARY OUTCOMES

The primary outcome will be a binary indicator of whether a child has reported (at least one episode of) either pain and/or sepsis during the follow up period. Not all children will be followed up for the same length of time and so the following analyses of the primary outcome will be considered:

1. Logistic regression. Dependent variable = whether there was a reported incidence of pain due to caries and/or sepsis during the period of follow up. Differences between dental practices included as a random effect. Length of follow up in years included as a covariate to allow for the variable length follow up. 97.5% confidence intervals will be generated for the difference between study treatment arms expressed as an odds ratio.

2. Analysis of time to first event (pain due to caries or sepsis) using a Cox proportional hazards model. Treatment groups will be compared pairwise. Results will be given in the form of 97.5% confidence intervals for the hazards ratio.

3. Analysis of the number of episodes at which pain due to caries and/or sepsis is reported using negative binomial regression. The dependent variable is the total number of episodes reported by a child; the number of months of follow up will be included as an exposure variable.

4.2 SECONDARY OUTCOMES

A number of secondary outcomes will be measured during the period of follow up. The frequency of measurements is described in Appendix 1.

4.2.1 Quantitative measures

These include:

- Incidence of caries in primary and secondary teeth – net score of caries over period of study;
- Quality of Life – mean QOL scores by child and group;
- Costs and cost-effectiveness – cost per child and incremental cost per pain/sepsis episode; and
- Acceptability of treatment strategy and associated experiences of participants and parents – MCDASf and VAS (child and parent); mean score and change in score over period of study.

4.2.2 Qualitative measures

Descriptive analysis will be carried out for acceptability of treatment strategy to the child and experiences of children and parents. For dentists preferences, all focus groups and interviews will be recorded and transcripts analysed using content analysis as described by Huberman and Miles (19). Content analysis is used as a means of analysing the content of people's communication and varies in its degree of abstraction and conceptualisation ranging from a simple word count and examining the manifest content of the words spoken to higher levels of conceptualisation (latent content).

Quantitative secondary outcome data will be analysed using multilevel models (repeated measures nested within children nested within general dental practices) using an appropriate error structure (binomial for binary variables, normal for continuous variables). Variation between dental practices, variation between children and variation between occasions will be modelled as random effects; difference between groups will be included as fixed effects. Length of follow-up in years will be included as a covariate to allow for the variable length follow-up. Within this framework we will be able to estimate:

1. The mean difference between groups at the end of the follow up period;
2. The mean difference between groups across the whole of the follow up period; and
3. The difference in the rate of change of the outcome across the follow up period

For each outcome the primary comparison of interest will be specified in the statistical analysis plan which will be finalised prior to completion of data collection.

4.2.3 Economic Analysis

Costs of the intervention: the CRF will collect information on treatments undertaken, staff grade (e.g. GDP or dental therapist) and treatment times. The resources used to provide the interventions will be calculated via a micro costing study based on time and material used to provide the interventions. This will include the use of all equipment used, consumables and staff costs. In addition to the micro costing study, unit costs will also be derived from routine data sources such as FFS in Scotland and UDA values in England.

Costs of subsequent care: the number of scheduled and unscheduled visits and treatments undertaken in the follow-up period will also be collected via the CRFs. The costs of onward referral will be obtained from existing data available within the NHS and appropriate unit costs applied.

Participant costs: participant costs will comprise of three main elements, productivity costs (e.g. time off work) additional child care costs and use of non-prescription medication as a result of tooth pain. This information will be collected every time a child visits the dentist during the trial follow-up period. Relevant unit costs will be applied, using routine data sources.

Cost-effectiveness: the economic evaluation will be based on a within trial analysis. The incremental cost per sepsis free patient (in comparison to usual care) and incremental cost per pain free patient (in comparison to usual care) will be calculated. Data collection from the trial will focus on estimating resource use, obtained from the CRFs and participant completed questionnaires administered at every dental visit. Unit costs will be based on nationally available data (UDA and FFS) and study specific estimates (micro costing study).

The analysis will use estimates of costs and effects estimated for each trial participant to calculate the incremental cost-effectiveness ratios for the follow-up period. Where appropriate the analysis will mirror the statistical analysis. The perspective of the analysis will be the patient and the care provider. The results of the analyses will be presented as point estimates of mean incremental costs and effects. Sensitivity analysis will be used to assess the robustness of the results to realistic variations in the levels of the underlying data. In addition, techniques such as bootstrapping will be used alongside sensitivity analysis to address uncertainty. Data will be presented as cost-effectiveness acceptability curves (CEACs).

4.3 END OF STUDY

End of the FiCTION trial is defined as the last patient at their last visit.

5 SERIOUS ADVERSE EVENTS

5.1 DEFINITIONS

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation (for longer than 24 hours), or prolongation of existing participants' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 SERIOUS ADVERSE EVENTS

Due to the type of study non-serious Adverse Events will not be recorded. However all Serious Adverse Events will be reported to the Newcastle Clinical Trial's Unit within 24 hours of the PI learning of its occurrence by using a secure fax line.

The initial report should contain the following minimum information*:

1. Study identifier (Protocol number)
2. Participant's unique study number
3. Date of birth
4. Event description
5. Start date of event
6. Reason for seriousness (i.e. death, life-threatening, hospitalisation, disability/incapacity or other)
7. Reporters name, signature & date

*In the case of incomplete information at the time of the initial reporting, all appropriate information should be provided as follow-up as soon as it becomes available.

Hospitalisations for elective treatment of a pre-existing condition do **not** need reporting as SAEs. Unrelated hospitalisations will be elicited at the follow-up appointment, scheduled subsequent appointments and all unscheduled/emergency appointments.

All SAEs will be reported to the MREC where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence (see 11.1.1)

Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies.

The Sponsor will be notified of all SAEs at the point of reporting to MREC by NCTU.

Contact details for reporting SAEs
Fax: 0191 208 8901, attention NCTU FiCTION Trial Manager

6 REGULATORY ISSUES

6.1 ETHICS APPROVAL

The conduct of this study will be in accordance with the ethical principles set out in the Declaration of Helsinki (2008).

Ethical and R&D approval of the protocol will be sought prior to commencement of the study. Local approvals (site specific assessments) will be sought before recruitment commences at each site (general dental practice).

6.2 CONSENT

The parent(s)/legal guardian(s) of all children in the study will provide written informed consent before any study procedures are carried out and a participant information sheet and parent information sheet will be provided to facilitate this process. In so far as possible, and with the agreement of the parent(s)/legal guardian(s), participating children will also be asked to provide written or oral assent. Those not competent in English will be invited to bring an interpreter with them to the recall appointment or to request an NHS interpreter where this service is available.

As part of the consent process, parent(s)/legal guardian(s) must agree to researchers & regulatory representatives having access to their child's dental records for monitoring and audit purposes.

Parent(s)/legal guardian(s) will also be informed that they have the right to withdraw from the study at any time. The right to refuse to participate without giving reasons will be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so will be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants will be free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Due to the pragmatic nature of the FiCTION study our follow up schedule is based upon the practice recall schedule. This can lead to issues regarding parents only taking their children to their dentist when there is a problem; when parents think that their child's teeth are fine they don't see the need to attend for routine check-ups. This means we risk losing valuable primary and secondary outcome data.

To this end we have developed a questionnaire for each non-attending child/parent that has not attended a follow up for 18 months or not attended their 36 month follow up. This questionnaire will be sent out by the practice to capture the reason for non-attendance and as much of data that would normally be collected through the corresponding visit questionnaire that we deem practicable to ask of non-attending families (or in the case of serial non-attenders, the data corresponding to final visit).

Normally, in the case of such amendments, participants would be re-consented to the amended protocol. However, it was felt that this may unduly overburden families (particularly since those concerned are by definition less engaged with the study) and the ethics committee have agreed to a process of implied consent.

Return of a completed questionnaire will be taken as indicative of implied consent by the family to provide outcome data in this way. If a questionnaire is not returned or returned blank, we will infer that the family does not wish to be contacted in this manner, does not wish to provide outcome data in this way and does not wish to be contacted in this way again. This information

will be passed to the practice with the instruction not to post out questionnaires in the future. If a questionnaire is returned partially completed then if required the practice will attempt to retrieve the missing information from the family. No reminders will be sent in the case of nonresponse.

6.3 CONFIDENTIALITY

The Chief Investigators will preserve the confidentiality of participants in the study and the Sponsor organisation will ensure that the study is registered under the Data Protection Act.

6.4 MONITORING RECRUITMENT/ RETENTION

Recruitment and retention rates will be monitored by the Trial Manager in the Newcastle Clinical Trials Unit and reported at DMEC meetings (or more regularly if requested) and at Trial Steering Committee meetings. In addition, there will be monthly reports to HTA.

6.5 INDEMNITY

Indemnity in respect of negligent conduct will be covered by the individual GDPs professional indemnity arrangements. Indemnity in respect of protocol authorship will be provided through a Dundee/Glasgow, Newcastle, Leeds/Sheffield, Cardiff and London Universities' public liability insurance. Indemnity in respect of study management will be provided by the University of Dundee, in its role as sponsor. There is no provision for indemnity in respect of non-negligent harm.

6.6 SPONSOR

University of Dundee will act as the main sponsor for this study. Delegated responsibilities will be assigned to the Newcastle Clinical Trials Unit.

6.7 FUNDING

The NIHR HTA is funding this study. As the setting for this trial is general dental practice and data collection is taking place within the "normal" appointments that these participants would be attending anyway there is no provision to reimburse participants for taking part in the study.

6.8 AUDITS

The study may be subject to inspection and audit, as part of their routine 10% or 'for cause' by the University of Dundee under their remit as sponsor and by other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

6.9 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Newcastle Clinical Trials Unit.

7 PUBLICATION POLICY

The results of the study will be published as a report for the NIHR HTA, and may be published as research papers in academic journals. Each of the participating PIs will be eligible for authorship on the NIHR HTA report. The CI (Jan Clarkson) will be first author on the NIHR HTA report. The study may be presented at scientific conferences and other similar events. No individual patient participating in the trial will be identified from any study report. Authorship on peer-reviewed publications arising from this definitive patient randomised trial will include the Chief Investigators, grant co-applicants and members of the clinical trials coordinating team (statistician & Trial Manager). The NIHR HTA will be acknowledged on each publication.

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9 APPENDICES

9.1 APPENDIX 1: SCHEDULING OF EVENTS

Event	Completed by:	Baseline examination appointment	Treatment appointments (Scheduled treatment or recall & unscheduled/ emergency)	Non-attendance postal questionnaires	Final appointment
Bitewing Radiographs	GDP		Risk-based in line with guidance. **NOT A STUDY INVESTIGATION**		
Consent/Assent	GDP	X			
ICDAS (CRF)	GDP	X			X
Pain: post treatment questions to GDP (CRF)	GDP		X		X
Cooperation (CRF)	GDP		X		X
Intervention Cost data (CRF)	GDP		X		X
Discomfort during treatment DDQ8	Parent		X	X	X
Quality of Life	Parent	X		X	X
Worry and Pain pre/post treatment questions to parent	Parent		X	X	X
Economic questions	Parent		X	X	X
MCDAS & worry	Child	X	X	X	X
Pain: pre/post treatment questions to child: VAS	Child		X	x	X

9.2 APPENDIX 2: AMENDMENT HISTORY

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
AM06	2.0	24/7/2014	Mark Palmer	There is an addition to the protocol section 2.14 Participant Timeline Which reads: If a participant fails to attend a scheduled or final appointment the practice will post the appropriate time point questionnaire with covering letter and prepaid envelope to the participant for completion (see 3.2 Data Management).
AM12	3.0	10/04/2015	Mark Palmer	Update of Trial Sites/Participant Timeline sections. Adding new site areas and removing mention of site numbers.
AM12	3.0	10/04/2015	Mark Palmer	Study Timescale section updated to reflect HTA approved extension to study.
AM12	3.0	10/04/2015	Mark Palmer	Update of contact information in Protocol contacts & Personnel. PI Protocol Signature Page removed.
AM12	3.0	10/04/2015	Mark Palmer	Section 1.4 mention of follow up changed from three years to up to three years.
AM12	3.0	10/04/2015	Mark Palmer	Update of Study Setting (2.1)/Recruitment of Practices (2.4) sections. Adding new site areas and removing mention of site numbers and recruitment period specific length
AM12	3.0	10/04/2015	Mark Palmer	Target Sample Size (2.7) updated to reflect altered sample size data due to HTA extension
AM12	3.0	10/04/2015	Mark Palmer	Identification and Recruitment of Participants (2.11) & Participant Randomisation (2.12) Section updated to reflect updated sample size and extended recruitment period specific length removed.
AM12	3.0	10/04/2015	Mark Palmer	Retention of Participants (2.13) addition of following text: We are also distributing leaflets and posters for display in practice waiting rooms to convey our thanks to the FiCTION families for their participation, while enhancing the trial's prominence within practices, sending the children birthday cards (see Appendix 10) via the practice as well as maintaining feedback from practices in order to guide development of suitable FiCTION branded merchandise promoting the study.
AM12	3.0	10/04/2015	Mark Palmer	Figure 2 Flow Diagram of Main Trial updated to reflect updated sample size and extended recruitment period.
AM12	3.0	10/04/2015	Mark Palmer	Serious Adverse Events (5.5) Removal of reference to Adverse Event recording and SAE contact number updated.
AM12	3.0	10/04/2015	Mark Palmer	Consent (6.2) addition of questionnaire implied consent explanation.
AM12	3.0	10/04/2015	Mark Palmer	Appendix 1 study letters, Appendix 3 Adverse Events, Appendix 4 Questionnaires, Appendix 5 Letter of Invitation, Appendix 6 Information Sheets, Appendix 7 Consent and Assent Forms, Appendix 8 Letter for GMP, Appendix 9 Poster, Appendix 10 Membership Card/ Birthday Card and references removed as not necessary.

AM12	3.0	10/04/2015	Mark Palmer	Appendix 2 Amendment History added
AM12	3.0	10/04/2015	Mark Palmer	Addition of study specific estimates of unit costs as a secondary outcome measure.
AM12	3.0	10/04/2015	Mark Palmer	Section 2.6 Principal Investigator changed to Practice Leads
AM12	3.0	10/04/2015	Mark Palmer	Section 2.10 Withdrawal criteria updated and two withdrawal options removed to bring in line with the trial.
AM12	3.0	10/04/2015	Mark Palmer	Section 7 publication policy updated.
AM12	3.0	10/04/2015	Mark Palmer	Section 4.1 Primary Outcomes & Section 4.2 Secondary Outcomes updated with more detail regarding statistical analysis.
AM12	3.0	10/04/2015	Mark Palmer	Section 2.5/3.1/4.2 Length of follow up (3 year) removed.
AM14	4.0	11/09/2015	Claire Macdonald	Section 2.11 Identification of participants additional information included on consent for future studies.

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