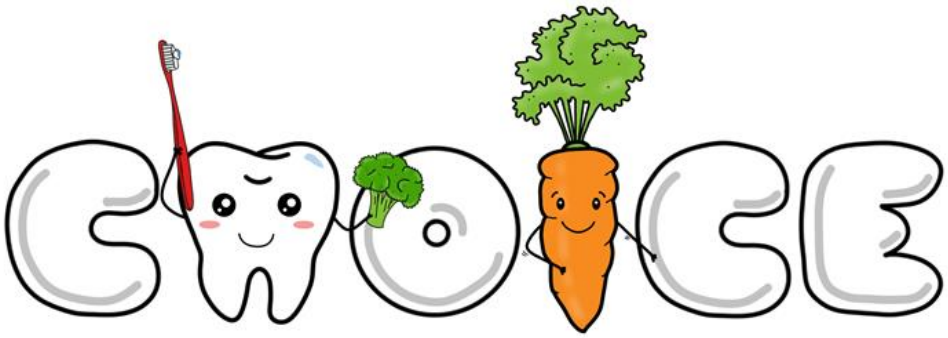

Changing Habits tO Prevent ChIld CariEs (CHOICE): A Randomised Controlled Trial of a Family- Focused Therapeutic Conversation Delivered by Dental Nurses in Primary Care

CHOICE Protocol
V2.0, 08.02.2024

Study Sponsor(s):

QUEEN'S UNIVERSITY BELFAST

University Road,

Belfast BT7 1NN

ISRCTN no.: 87811904

Research Ethics Ref: 23/WM/0056

Sponsor Ref: B21/21

Funder Ref: NIHR131817

The CHOICE trial is funded by the NIHR Health Technology Assessment Programme (Award ID: NIHR131817*), ENCOURAGE sub study is an EME Mechanistic study embedded in the main trial NIHR151317 . The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care*.

Protocol Approval

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

Authorised by Chief Investigator:

Signature: _____ **Date:** _____

Professor Pauline M Adair
Professor of Clinical and Health Psychology
Joint Programme Director, Doctorate in Clinical Psychology
Queen's University Belfast

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

Authorised on behalf of Sponsor:

Signature: _____ **Date:** _____

Ms Kathryn Taylor
Research Governance Manager
Queen's University Belfast

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

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:** _____

Dr Girvan Burnside
Reader in Biostatistics
Liverpool Clinical Trials Centre,
University of Liverpool

General Information

This document describes the CHOICE trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Professor Pauline Adair, via the Liverpool Clinical Trials Centre (LCTC).

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

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

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in Section 15.

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

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ENCOURAGE Sub-study
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Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	
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Additional Contacts:

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

Contact	**Document Title**
Independent Data and Safety Monitoring Committee (IDSMC) Trial Steering Committee (TSC) Trial Management Group (TMG)	CHOICE Trial Oversight Committee Membership Log

1 Table of Contents

2 Glossary

AE	Adverse Event
BSA	Business Services Authority
BSO	Business Services Organisation
CI	Chief Investigator
COM-B	Behaviour Change Wheel
CRF	Case Report Form
CTU	Clinical Trials Unit
DR-BNI	Dental Recur Brief Negotiated Interview
EAP	Economic Analysis Plan
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
GCP	Good Clinical Practice
GDP	General Dental Practitioner
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
LCTC	Liverpool Clinical Trials Centre
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NRES	National Research Ethics Service
ONS	Office for National Statistics
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
PAS	Patient Administration System
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
RSO	Research Support Office
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SES	Socio-economic Status
SDV	Source Data Verification
SOP	Standard Operating Procedure
SWAT	Study within a Trial
TDF	Theoretical Domains Framework
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TPB	Theory of Planned Behaviour
TSC	Trial Steering Committee
USMs	Urgent Safety Measures

3 Protocol Overview

Full Title:	**C**hanging **H**abits t**O** Prevent Ch**I**ld **C**ari**E**s (**CHOICE**): A Randomised Controlled Trial of a Family-Focused Therapeutic Conversation Delivered by Dental Nurses in Primary Care
Acronym:	CHOICE
Phase:	III
Target Population:	Children (male and female) aged 3-7 years old, with at least one carious lesion into dentine, attending 40 general dental practices in four regions of the UK (Northern Ireland, East of England, Yorkshire and the Humber, The North West of England).
Sample size:	908
Inclusion Criteria:	1. Child has at least one carious lesion into dentine 2. Aged ≥3 years and <8 years at the time of randomisation 3. Child is receiving NHS dental care 4. The intervention can be delivered in a comprehensible way to the child's parent/primary caregiver 5. Written and informed consent obtained from child's parent/primary caregiver and agreement to comply with the requirements of the study
Exclusion Criteria:	1. Child presents with advanced caries that require referral for extractions 2. Child presents with only arrested carious lesions into dentine in primary teeth [arrested as defined within national epidemiological criteria] 3. Child is living in the same household as someone already recruited to the CHOICE Trial.
Study Centres and Distribution:	40 general dental practices in four regions of the UK (N. Ireland, East of England, Yorkshire and the Humber, The North West of England)
Individual Participant Trial Duration:	24 months following randomisation (+/- 3 months)
Study Duration:	42 months (recruitment is planned to take place over a period of 18 months with 24 months (+/-3 months) follow up per participant)

Intervention:	**Intervention:** A therapeutic conversation, the Dental Recur Brief Negotiated Interview (DR-BNI) of around 30 minutes using a personalised goal centred approach to guide parents/primary caregivers to change habits that lead to tooth decay in favour of promoting oral health routines; and usual care. **Control:** Usual care
Objectives:	
Primary objectives	1. To compare the novel technology of the dental nurse-delivered DR-BNI and usual care versus usual care alone provided in NHS primary dental care on the development of dental caries over a two-year period in children aged 3-7 years at recruitment.
Secondary objectives:	2. To evaluate the effect of delivering DR-BNI and usual care two years after DR-BNI intervention on: number of teeth with caries experience, episodes of dental pain, number of fillings, extractions, reported child oral health behaviours (sugar control, tooth brushing, dental attendance), and parental attitudes towards these behaviours.
Economic objectives:	3. To compare the costs and benefits within a cost-effectiveness framework of DR-BNI and usual care with usual primary dental care alone. 4. To determine the long-term benefits and cost benefits of the DR-BNI intervention in primary dental care by following the index child and siblings' dental records for up to 10 years from end of study.

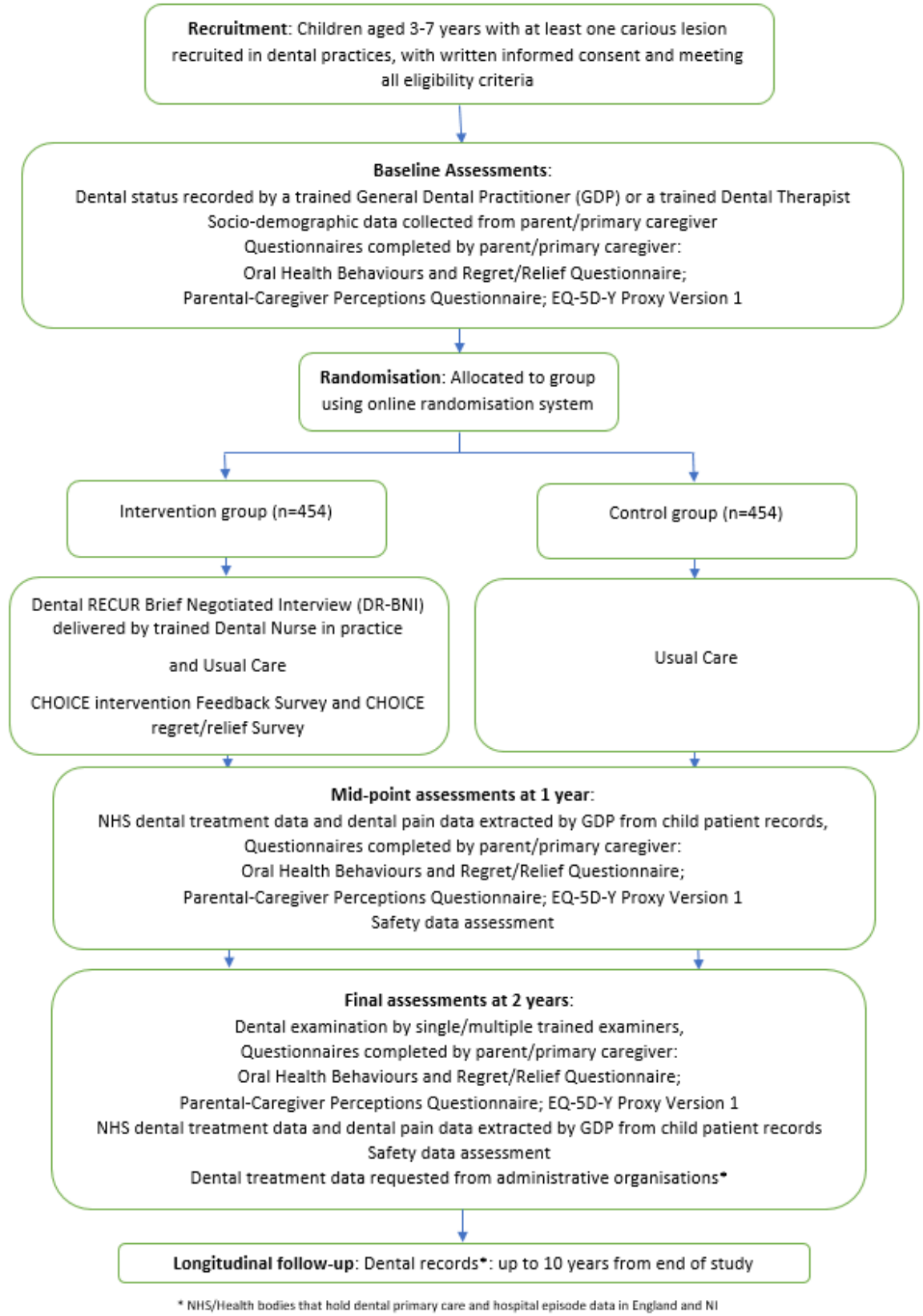
Exploratory/ Translational objectives:	5. To explore facilitators and barriers to recruitment of the target population informed by the Behaviour Change Wheel (COM-B). 6. To determine if a motivational letter and oral health toolkit intervention enhance recruitment to the CHOICE Trial in irregular dental-attending children 7. To understand processes of behaviour change including fidelity, dose and reach of the DR-BNI intervention. 8. To consider comparative dental health outcomes and reported child oral health behaviours in children from different ethnic groups, with ethnicity self-defined by families using ONS Census 2021 descriptors, for families who receive DR-BNI and usual care and those in the usual care alone group. 9. To understand how to enhance implementation of DR-BNI in primary dental care informed by the Theoretical Domains Framework (TDF) through process evaluation involving patients, parents, families and the dental team. 10. To explore potential mediators (parental self-efficacy and regret/relief) of the effect of DR-BNI on caries experience 11. To examine the role of parents' experience and anticipation of counterfactual emotions such as regret and relief in engaging and benefitting from the DR-BNI intervention.
ENCOURAGE substudy (EME Mechanistic study NIHR151317) objectives	12. To quantify salivary levels of lactic acid at baseline, and at 6 months follow-up, and determine if change in lactic acid concentration contributes towards the effect of intervention versus control on the caries outcome at 2 years. 13. To quantify salivary levels of pyruvic acid, citric acid, 2-ketoglutamic acid, succinic acid, malic acid and fumaric acid at baseline, and at 6 months follow up, and determine if changes in these levels contribute towards the effect of intervention versus control on the caries outcome at 2 years. 14. To determine if salivary acid levels correspond with microbiome eubiosis or dysbiosis by studying the oral bacterial microbiome and fungal mycobiome in a subset of 60 children at baseline, and at 6 months follow up.

Outcomes:		**Corresponding Objective:**
Primary outcome:	1. Caries experience (measured at dentinal level) at 24 months post-randomisation in any tooth which was caries free or unerupted at baseline	1, 8, 10, 11
	2. Number of teeth (caries free or unerupted at baseline) with caries experience into dentine 24 months post-randomisation.	2, 8

Secondary Outcomes:	3. Parent reported attitudes to child oral health behaviours (seven subscales)	2, 8, 10, 11
	4. Parent reported child oral health behaviours (four measures)	2, 8
	5. Episodes of dental pain	2
	6. Number of filled teeth (caries free or unerupted at baseline) 24 months post randomisation	2
	7. Number of extracted teeth (caries free or unerupted at baseline) 24 months post randomisation	2
Economic outcomes:	8. Health related quality of life (EQ-5D-Y)	3
	9. Oral health related quality of life (Parental-Caregiver Perceptions Questionnaire)	3
	10. Costs of treatment	3, 4
SWAT outcomes:	11. Attendance for a dental checkup	6
	12. Recruitment into the CHOICE trial	6
Qualitative outcomes:	13. Fidelity to the DR-BNI	7
	14. Number and type of goals chosen; behaviour techniques used	7
	15. Facilitators and barriers to recruitment of the target population	5
	16. Implementation of DR-BNI	9
ENCOURAG Eoutcomes	17. Salivary levels of lactic acid at randomisation visit (baseline) and at 6 months follow up	12
	18. Salivary levels of pyruvic acid, citric acid, 2-ketoglutamic acid, succinic acid, malic acid and fumaric acid at randomisation visit (baseline) and at 6 months follow up	13
	19. Comparison of salivary acid levels with microbiome eubiosis or dysbiosis	14

3.1 Schematic of Study Design

CHOICE Flow Diagram



4 Roles and Responsibilities

4.1 Sponsor

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

4.2 Funder

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme.

Funder(s)	Financial and Non-financial Support Given	Role
NIHR Health Technology Assessment Programme	Non commercial financial support for delivery of project	This project (project reference NIHR131817) is funded by the NIHR Health Technology Assessment Programme. NIHR will monitor progress against key milestones via the submission of regular progress reports

There is also the embedded ENCOURAGE sub-study,

4.3 Chief Investigator

Professor Pauline Adair is the Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team. Professor Adair will lead on training for the delivery of the intervention and on the process evaluation. Joint Lead Applicant Dr Girvan Burnside will lead on recruitment and data quality and has a joint role as the Lead Statistician.

4.4 Principal Dental Lead, Regional Dental Leads and Principal Investigators

In each Region, a Regional Dental Lead has been identified. There are Regional Dental Leads in East of England, The North West of England, Yorkshire and the Humber and Northern Ireland. The Regional Dental Leads will work with the Principal Dental Lead (Co-Investigator, Professor Cynthia Pine) to identify, recruit and support participating centres (general dental practices). In each participating centre, a Principal Investigator (a general dental practitioner) will be identified to be responsible for identification, recruitment, data collection and completion of electronic CRFs, along with follow up of study patients and adherence to the study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

4.5 Clinical Trials Unit

Liverpool Clinical Trials Centre (LCTC) at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, safety reporting, data management, randomisation, statistical analysis and participating site coordination.

4.6 School of Psychology (Central Research Team)

The CHOICE team at the School of Psychology in Queens's University Belfast will have management responsibility for trial related activities including (but not limited to) trial process evaluation and embedded qualitative work as well as the study within a trial (SWAT), budget administration, some aspects of training and site set up, ongoing support and communication with participating sites, follow up of and keeping in touch with trial participants.

4.7 School of Medicine, Dentistry and Biomedical Sciences (ENCOURAGE Research Team – EME Mechanistic Study NIHR151317)

The ENCOURAGE team at the School of Medicine, Dentistry and Biomedical Sciences in Queens's University Belfast will work together with the CHOICE team in the School of Psychology, to manage ENCOURAGE trial related activities including (but not limited to) budget administration, some aspects of training, ongoing support and communication with participating sites, and sample management and shipment for ENCOURAGE.

4.8 Oversight Committees

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

4.8.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required.

4.8.2 Trial Steering Committee (TSC)

The Trial Steering Committee will monitor the trial against milestones and advise on methodological aspects and implementation issues. The TSC will consist of an independent chairperson, 2 independent experts in the field of oral health behaviour change, a statistician, including the CI and observers. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairperson. The decision for the continuation of the trial lies with the TSC and as such they will meet throughout the trial (at least annually).

4.8.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) will consist of an independent chairperson, plus 1 independent member; who is an expert in the field of dental public health, and an independent statistician. The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial

conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually).

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study.

The above oversight committees will also oversee the ENCOURAGE study which is a sub-study of CHOICE.

4.9 Protocol Contributors

Name	Affiliations	Contribution to protocol
Professor Pauline Adair	Queen's University, Belfast	Protocol development, clinical and scientific arrangements, governance arrangements trial conduct
Dr Girvan Burnside	University of Liverpool	Protocol development, statistical lead, trial design and conduct.
Professor Cynthia Pine	Kippax Design Ltd	Protocol development, quality and governance processes to deliver baseline and final dental assessment outcomes.
Professor Ciaran O'Neill	Queen's University, Belfast	Health Economics, protocol development.
Mrs Catherine Spowart	University of Liverpool	Protocol development, governance arrangements and trial conduct.
Dr Marc Edwards	Queen's University, Belfast	Protocol and SWAT development.
Mrs Joanne Nanson	University of Liverpool	Protocol development.
Ms Eleanor Macdonald	University of Liverpool	Protocol development
Professor Fionnuala Lundy	Queen's University, Belfast	ENCOURAGE Sub-study

5 INTRODUCTION

5.1 Background

Child dental caries continues to be a problem in the UK despite considered efforts to ameliorate it; with a higher prevalence in deprived communities reflecting the social determinants of health (Public Health England, 2017). Public Health England's 2015 survey of 5-year-old children found 25% had experienced tooth decay, having 3 or 4 teeth affected. In the slightly later 2017 survey, 23% of 5-year-old children had tooth decay and those from deprived backgrounds had higher levels of decay (34%) than those who were least deprived (14%), a finding that appears to have changed little in between surveys (Public Health England, 2019). Prevention of child dental caries is a policy priority across the UK while dental extraction is the leading cause of hospital admission for children aged 5-9 years (Goodwin et al., 2015b). Dental caries that are left untreated in children can develop into a serious health condition and may result in admission to hospital for tooth extraction under a general anaesthetic, which may be the child's first experience of dental treatment. Other problems include insomnia, pain and days lost to school so its impact can be significant for the family (Goodwin et al., 2015b, Goodwin et al., 2015a).

The CHOICE Trial focuses on supporting families to set personalised goals that lead to the adoption of healthy behaviours relevant to improving their child's oral health and which can become part of new daily routines within the family setting. The intervention is based on an alcohol screening brief intervention which has been shown to be effective and cost-effective in reducing alcohol intake (Bernstein et al., 2007, Barbosa et al., 2015) The result is that this leads to healthier habits that are long lasting and given the family focus of the CHOICE trial, the whole family can potentially benefit. The CHOICE Trial delivers a brief behaviour change intervention (the Dental RECUR – Brief Negotiated Interview; DR-BNI) that provides a supportive goal-centred approach to teach and motivate primary caregivers (usually a parent), as the key agents of behaviour change in families, to change old habits that lead to tooth decay (lack of twice daily tooth brushing and sugar in the diet) in favour of health promoting habits. The delivery of the intervention in a supportive and non-judgemental way using the principles of Motivational Interviewing is crucial to its success as demonstrated in the Dental RECUR trial (Pine et al., 2020). The key strategy here is to promote environmental and personal change within the family setting by supporting the adoption of healthier choices that are proven to reduce dental caries by taking small steps and agreeing a minimum of two goals for behaviour change. Telling a parent/primary caregiver that their child has dental disease and is at future risk of further disease can be a teachable moment, as the parent is likely to have a heightened emotion and may anticipate regret from not changing the future (Brewer et al., 2016, Ellis et al., 2018). While on its own, information on disease risk is not sufficient for behaviour change, when followed with positive behavioural support and resources for behaviour change, then change and prevention of future caries is more likely as demonstrated in the Dental RECUR trial (Pine et al., 2020). One mechanism here may be parental self-efficacy (confidence) to make the changes agreed (Adair et al., 2004).

5.2 Rationale

No trial of a behavioural intervention to change family habits for children, that is delivered by dental nurses in a face-to-face format with parents, has been carried out within primary dental care. The CHOICE Trial focuses on supporting families to set personalised goals that lead to the adoption of healthy behaviours relevant to improving oral health and which can become part of new daily family routines. Our previous Dental RECUR trial recruited children scheduled for dental extractions and found a 29% decrease (p=0.021) in the relative risk of new caries for DR-BNI group compared to control (Pine et al., 2020). Two thirds of the children re-attended the dental practice that referred them for extractions; and 40% of children in the control group had at least one dental restoration in the subsequent two-year period compared to only 22% in the intervention, DR-BNI group. As indicated above, sugar habits represented most of the goals chosen by parents. Given these benefits, it is important to test if the intervention, DR-BNI delivered in the Dental RECUR trial can be effective earlier in the disease process to prevent at-risk children in primary care needing more invasive treatments including extractions under general anaesthetic, which carries an additional risk. Piloting of new primary care contracts in England identifies that evidence is needed of how to implement effective prevention using skill mix (Robinson et al., 2019).

5.3 Risk and Benefits

5.3.1 Potential Risks

The intervention involves an interview using a personalised goal-centred approach to guide parents/primary caregivers on how to change habits that lead to tooth decay in favour of health promoting family routines. A trained dental nurse delivers the intervention face-to-face. It is possible that parents/primary caregivers may become upset when discussing their child's dental health. It is also possible that safeguarding issues could be disclosed during the intervention, and this will require the following of local guidance by the dental practices.

5.3.2 Potential Benefits

The CHOICE trial intervention may lead to the adoption of healthy behaviours relevant to improving children's oral health. The healthy behaviours can become part of new daily routines within a family setting which can result in healthier habits that are long lasting, and the whole family can potentially benefit. The intervention may prevent at-risk children in primary care needing more invasive dental treatments including extractions under general anaesthetic.

6 AIMS

6.1 Objectives:

6.1.1 Primary objective:

1. To compare the novel technology of the dental nurse-delivered DR-BNI and usual care versus usual care alone provided in NHS primary dental care on the development of dental caries over a two-year period in children aged 3-7 years at recruitment.

6.1.2 Secondary objectives:

2. To evaluate the effect of delivering DR-BNI and usual care two years after DR-BNI intervention on: number of teeth with caries experience, episodes of dental pain, number of fillings, extractions, reported child oral health behaviours (sugar control, tooth brushing, dental attendance), and parental attitudes towards these behaviours.

6.1.3 Economic objectives:

3. To compare the costs and benefits within a cost-effectiveness framework of DR-BNI and usual care with usual primary dental care alone.

4. To determine the long-term benefits and cost benefits of the DR-BNI intervention in primary dental care by following the index child and sibling's* dental records for up to 10 years from end of study.

6.1.4 Exploratory/ Translational objectives:

5. To explore facilitators and barriers to recruitment of the target population informed by the Behaviour Change Wheel (COM-B).

6. To determine if a motivational letter and oral health toolkit intervention enhance recruitment to the CHOICE Trial in irregular dental-attending children

7. To understand processes of behaviour change including fidelity, dose and reach of the DR-BNI intervention.

8. To consider comparative dental health outcomes and reported child oral health behaviours in children from different ethnic groups, with ethnicity self-defined by families using the Office for National Statistics (ONS) Census 2021 descriptors, for families who receive DR-BNI and usual care and those in the usual care alone group.

9. To understand how to enhance implementation of DR-BNI in primary dental care informed by the Theoretical Domains Framework (TDF) through process evaluation involving parents/primary caregivers and the dental team.

10. To explore potential mediators (parental self-efficacy and regret/relief) of the effect of DR-BNI on caries experience

11. To examine the role of parents' experience and anticipation of counterfactual emotions such as regret and relief in engaging and benefitting from the DR-BNI intervention.

12. To quantify salivary levels of lactic acid at baseline, and at 6 months follow-up, and determine if change in lactic acid concentration contributes towards the effect of intervention versus control on the caries outcome at 2 years.

13. To quantify salivary levels of pyruvic acid, citric acid, 2-ketoglutamic acid, succinic acid, malic acid and fumaric acid at baseline, and at 6 months follow up, and determine if changes in these levels contribute towards the effect of intervention versus control on the caries outcome at 2 years.

14. To determine if salivary acid levels correspond with microbiome eubiosis or dysbiosis by studying the oral bacterial microbiome and fungal mycobiome in a subset of 60 children at baseline, and at 6 months follow up.

*Siblings are defined as being aged up to 11 years at study entry, living in the same household and who attend the same dental practice as the index child.

6.2 Outcomes

Outcome	Timing of measurement	Method of measurement	Objective
Primary outcome			
Caries experience (measured at dentinal level) at 24 months post-randomisation in any tooth which was caries free or unerupted at baseline	Baseline and 24 months (+/-3 months post randomisation).	Dental status examination to national standards as used in UK Dental Epidemiology Surveys of Child Dental Health	1, 8, 10, 11
Secondary outcome(s)			
Number of teeth (caries free or unerupted at baseline) with caries experience into dentine 24 months post-randomisation.	Baseline and 24 months (+/-3 months post randomisation).	Dental status examination to national standards as used in UK Dental Epidemiology Surveys of Child Dental Health	2, 8
Parent reported attitudes to child oral health behaviours (seven subscales) • Parental efficacy in relation to child toothbrushing • Importance and intention to brush child's teeth • Parental efficacy in relation to controlling child sugar snacking	Baseline, 12 months and 24 months (+/- 3 months post randomisation).	Parent reported Oral Health Behaviours and Regret/Relief Questionnaire (OHB-RRQ)	2,8, 10, 11

• Importance and intention to control child sugar snacking • Perceived seriousness of tooth decay in children • Chance control – decay occurs by chance • Regret/Relief regarding child oral health behaviours			
Parent reported child oral health behaviours (four measures) • Level of toothbrushing • Sweets consumption • Sugary drinks consumption • Dental attendance	Baseline, 12 months and 24 months (+/- 3 months post randomisation).	Parent reported Oral Health Behaviours and Regret/Relief Questionnaire (OHB-RRQ)	2, 8
Episodes of dental pain	12 months and 24 months (+/- 3 months post randomisation).	From child dental treatment records of episodes of dental pain.	2
Number of filled teeth (caries free or unerupted at baseline) 24 months post randomisation	Baseline and 24 months (+/-3 months post randomisation).	Dental status examination to national standards as used in UK Dental Epidemiology Surveys of Child	2
Number of extracted teeth (caries free or unerupted at baseline) 24 months post randomisation	Baseline and 24 months (+/- 3 months post randomisation).	Dental status examination to national standards as used in UK Dental Epidemiology Surveys of Child	2
Economic outcomes			
Health related quality of life	Baseline, 12 months and 24 months (+/- 3 months post randomisation).	EQ-5D-Y Proxy Version 1; EQ-5D-Y Interviewer Administered Proxy Version 1; EQ-5D-Y Proxy REDcap, general dental practice records and administrative records	3
Oral health related quality of life	Baseline, 12 months and 24 months (+/- 3 months post randomisation).	Parental-Caregiver Perceptions Questionnaire (Marshman et al., 2005)	3
Costs of treatment	24 months, 10 years	Dental records of index child and siblings from administrative* records	3,4
SWAT outcomes			
Attendance for a dental checkup	During 18-month recruitment phase	Dental attendance records	6

Recruitment into the CHOICE trial	During 18-month recruitment phase	Recruitment data	6
Qualitative outcomes			
Fidelity to the DR-BNI	Intervention visit	Audio recordings of the DR-BNI Intervention/fidelity checklist	7
Number and type of goals chosen; behaviour techniques used	Intervention visit	Audio recordings of the DR-BNI intervention	7
Facilitators and barriers to recruitment of the target population	18-24 months from the start of the trial	Qualitative interviews	5
Implementation of DR-BNI	24-36 months from the start of the trial	Qualitative interviews	9
ENCOURAGE outcomes			
Salivary levels of lactic acid	Randomisation visit (Baseline) and 6 months (+/-1 month post randomisation).	Salivary metabolomics	12
Salivary levels of pyruvic acid, citric acid, 2-ketoglutamic acid, succinic acid, malic acid and fumaric acid	Randomisation visit (Baseline) and 6 months (+/-1 month post randomisation).	Salivary metabolomics	13
Bacterial and fungal microbiome	Randomisation visit (Baseline) and 6 months (+/-1 month post randomisation).	Internal Transcribed Spacer (ITS) ribosomal RNA (rRNA) for identification of fungi and 16S sequencing for identification of bacteria in saliva samples	14

*Administrative data sources include NHS Digital, NHS Business Services Authority (BSA), Business Services Organisation (BSO), Patient Administration System (PAS) or their successors.

7 TRIAL DESIGN

CHOICE aims to compare the clinical effectiveness and cost-effectiveness of the behavioural intervention DR-BNI in addition to usual care in 3–7-year-old children versus usual care alone. CHOICE is designed as a two-arm randomised controlled trial (RCT) and is an outcome assessor-blinded trial.

The trial will be conducted in general dental practices in four regions of the UK: The North West; East of England; Yorkshire and the Humber; and in Northern Ireland.

The primary outcome, measured 24 months (+/- 3 months) post randomisation, is the development of caries in any tooth which was caries free or unerupted at baseline.

The design includes an internal pilot to assess recruitment of practices and participants with pre-determined progression criteria to the main trial.

7.1 Blinding

Where possible, final dental assessments at 24 months (+/- 3) will be undertaken by a single, trained examiner who will be blind to child's group allocation. If a single examiner is not feasible, for example due to rapid recruitment, then a reserve plan will be used that will include a team of trained assessors, to undertake the final dental assessments. The examiner/s will be independent to the general dental practices and will not have access to documentation containing trial allocation.

7.2 Who is blinded

As mentioned in section 7.1, a blinded outcome assessor will complete the final dental assessment at 24 months (the 24-month final assessment). Dental practice staff at all participating practices, LCTC staff and participants will be aware of treatment allocation.

7.3 Trial Setting

Participants will be identified and recruited from up to 40 general dental practices in the UK; approximately 10 per region in: The North West of England; East of England; Yorkshire and the Humber; and in Northern Ireland. Follow up will occur within the same dental practices providing usual care for these patients.

7.3.1 Selection of Participating Sites

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

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the CHOICE trial and will be opened to recruitment upon successful completion of all global (e.g. REC) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

7.3.2 **Selection of Principal Investigators**

Principal Investigators will be required to demonstrate equipoise and commitment during early stage feasibility assessment. All Investigators will have the particular dental expertise necessary to conduct the study in accordance with the protocol and all regulatory and ethical requirements. Investigators will also be required to provide evidence of GCP training dated within 3 years at site initiation. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable Co-Investigator should be identified (where possible) at each site to deputise in case of PI absence.

8 ELIGIBILITY CRITERIA

The CHOICE trial aims to recruit 908 patients based on sample size calculations described in Section 13.2.1. Written, informed consent must be provided for all patients before any study procedures occur (see Section 10.2 for more information regarding informed consent processes) and they must meet all eligibility criteria as described below.

8.1 Inclusion Criteria

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

- Child has at least one carious lesion into dentine
- Aged ≥3 years and <8 years at the time of randomisation
- Child is receiving NHS dental care
- The intervention can be received in a comprehensible way by the child's parent/primary caregiver
- Written and informed consent obtained from child's parent/primary caregiver and agreement to comply with the requirements of the study

8.2 Exclusion Criteria

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

- Child presents with advanced caries that require referral for extractions
- Child presents with only arrested carious lesions into dentine in primary teeth [arrested as defined within national epidemiological criteria].
- Child is living in the same household as someone already recruited to the CHOICE Trial.

8.3 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials during their participation in CHOICE. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the CHOICE trial, this must first be discussed with the LCTC who will contact the Chief Investigator (Professor Pauline Adair).

9 TRIAL INTERVENTION

9.1 Introduction

Eligible participants will be randomised in a ratio of 1:1 to the DR-BNI or control.

CHOICE intervention: A personalised and tailored behavioural intervention, the Dental-RECUR Brief Negotiated Interview (DR-BNI), that has been developed by the Chief Investigator and shown to be effective and cost-effective in secondary care settings for children having dental extractions. Those who are randomised to the CHOICE intervention will return to usual care once the CHOICE intervention has been completed.

Control: Participants will be allocated to receive usual care that is provided by the dental practice at which they are recruited.

9.2 CHOICE Intervention GROUP

The DR-BNI intervention will take advantage of a "teachable moment" which is an opportunity created through dentist-parent/primary caregiver's interaction at the time of dental check-up where information about the health of their child's teeth is communicated (that is that their child has tooth decay). This can be used to encourage parents/primary caregivers to change unhealthy behaviours, especially when informed that their child has tooth decay. Up to 18 week window likely provides a teachable moment based on experience from our Dental RECUR trial so the DR-BNI intervention needs to be delivered within this timeframe however, the intervention should be completed within 12 weeks of randomisation. The intervention will primarily be delivered within the dental practice. If delivery face to face is prevented due to Covid-19 or a parent is unable to attend the practice for the intervention to be delivered, face-to-face (videocall) remote delivery online is allowed.

Participants randomised to the CHOICE Trial intervention will take part in a structured conversation (DR-BNI), lasting approximately 30 minutes, delivered by dental nurses using motivational interviewing with behaviour change techniques. It adopts a tailored and personalised approach taking account of parent/primary caregiver preferences for behaviour change. Three key dental behaviours (regular toothbrushing with a fluoridated toothpaste, sugar control and regular dental attendance) are communicated during an empathic and non-judgemental conversation and parents choose one or two behaviours they feel they can change for their child. These are set as goals that are specific, measurable, attainable, relevant and time-based (SMART) and aim to promote oral health. The intervention is delivered in six steps, each lasting around five minutes covering:

1. **Build Rapport.** Get the parent/primary caregiver's agreement to talk about the child's dental decay. Talk about the possible causes of tooth decay and ask which are the most relevant to their child.
2. **Pros and Cons.** Review child's oral health behaviours (e.g., sugar intake, brushing with fluoride toothpaste, regular dental attendance). Highlight discrepancies.
3. **Feedback.** Assess parent/primary caregiver knowledge, elicit permission, provide evidenced-based information about tooth decay.
4. **Readiness to Change.** Explore readiness to change using resources and offer information
5. **Action Plan.** Negotiate a goal and summarise discussion. Develop a plan of action/prescription for change based on parent/primary caregiver's ideas.
6. **Thanks, Summarise, and Feedback.** Summarise discussion, outline next steps, provide feedback questionnaires.

In the general dental practice setting, the trained dental nurses will meet with each parent/primary caregiver assigned to the intervention arm of the trial for the structured 30-minute conversation outlined above.

The dental nurses who deliver the intervention will have training provided by the CHOICE trial team. Dental nurses will attend a one-day workshop (in person or online) to learn how to deliver DR- BNI. The DR-BNI is a complex, multi-faceted and tailored intervention that requires training of the dental nurses in its discrete components as well as its unique philosophy and this is not routinely practiced in dentistry. Training is led by an independent experienced practitioner psychologist trained in motivational interviewing and behaviour change techniques.

Training will be theory and skills-based teaching including theory of behaviour change, practical motivational interviewing skills essential to deliver the DR-BNI intervention, and role-play/practice with supervision and feedback. The aim of the DR-BNI intervention is to focus on a forward and future based perspective where dental caries can be prevented in the future rather than dwelling on the past, which cannot be changed. Dental nurses will be expected to practise their skills following the training with a peer, who has also been trained, and provide one recording for fidelity check prior to delivering their first intervention. Training will be supported by a DR-BNI dental practice toolkit including a dental nurse intervention manual/video and patient facing materials which will be take-home resources given to participants by the dental nurses that reinforces goals and action planning for behaviour change.

As the DR-BNI is being delivered across 40 general dental practices with a minimum of one nurse trained in each practice, fidelity monitoring is planned based on a combination of criteria used in the Dental RECUR trial, the framework of Bellg and colleagues (Bellg et al., 2004). This focuses on three elements: 1) study design, 2) training the dental nurse interventionists, and 3) delivery, receipt and enactment of treatment skills during the intervention, and the framework proposed by Haynes and colleagues (Haynes et al., 2015) which is more suitable for novel, contextualised interventions such as the DR-BNI. This will provide a comprehensive measure of fidelity suitable for a personally tailored behaviour change intervention and taking account of dental nurse delivery style (therapist variables), all of which could influence the outcome. As all DR-BNI sessions will be recorded, we will be able to provide a comprehensive understanding of what was delivered and the quality of this. To ensure fidelity to the DR-BNI protocol, audio recordings will be checked for adherence to the intervention and additional supervision provided where adherence has not been met.

In addition to the DR-BNI, participants randomised to the intervention group will receive usual care from the site where they were recruited.

9.3 Control Group

For participants randomised to the control group, they will receive usual care from the site where they were recruited.

All participants recruited into the study (regardless of arm) will receive a free dental pack (containing a toothbrush and toothpaste) for their child.

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

A poster in the dental practice will inform patients that a research study is taking place at the site.

Child patients aged 3 to 7 years with at least one carious lesion into dentine, who attend a CHOICE dental practice, will be assessed to identify potentially eligible participants for the trial. An electronic screening log will be maintained by the CHOICE team of all the patients who undergo screening regardless of whether they are assessed as eligible or decide to participate in the trial, as this will provide important information for monitoring purposes. Reasons for not being eligible will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that parents/primary caregivers do not have to provide a reason unless they wish to do so. Parents/primary caregivers of potentially eligible patients will be informed about the CHOICE trial by their treating dental team and given a Participant Information Sheet and Consent form (PISC). If deemed preferable, the dental team also has the option to send out the PISC to potentially eligible participants by post or email. A telephone call or text can also be made to potentially eligible participants to discuss the trial with them before or after sending out the PISC. The PISC will explain what the CHOICE trial is and what it would involve if they decided to take part. Sufficient time will be provided to discuss the trial and decide whether or not they wish for them/their child to take part in the trial.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in LCTC coordinated trials. The process should involve discussion between the potential participant or their parent/primary caregiver and a CHOICE trained staff member, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants or their parent/primary caregiver to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. A separate consent form will be used for implementation interviews and sent by email/post to participants who agree to take part with a request to sign and return to The CHOICE Trial office in the School of Psychology, Queen's University, Belfast prior to any interview taking place. If a potential participant does not want to provide consent, they do not have to give a reason.

Following screening assessment, parents/primary caregivers for the identified child will be approached by the CHOICE trained staff during a dental appointment, or following a dental appointment, and invited to consider participating in the CHOICE trial. If deemed preferable, the dental team also has the option to send out the PISC to potentially eligible participants by post or email. Written informed consent will be sought from those who agree to participate, while allowing adequate time to consider enrolment into the trial prior to the baseline assessments being collected, randomisation and the DR-BNI being delivered. Where possible, to maximise participation in the trial, randomisation will take place at the same appointment as completion of baseline questionnaires and/or the delivery of the DR-BNI while adhering to the consort flow diagram.

A written participant information sheet that forms part of the ethically approved Participant Information Sheet and Consent form (PISC) will be provided. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The CHOICE trained staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise. Only after a full explanation has been given about the CHOICE Trial involvement, and any queries answered satisfactorily, should the eligible participant consent to the trial.

After verbal and written information has been provided, the individual seeking consent will ensure that the person with parental responsibility has fully understood all the information and will ask if they are happy to consent to participation in the trial. Where this is the case, an electronic consent form will be completed and signed/dated by the parent/primary caregiver. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

If an eligible participant decides that they would not like to make the decision at their child's current dental appointment, then adequate time will be given for the participant to make a decision before being approached again. The right of the eligible participant to refuse consent to participate in the trial without giving reasons will be respected.

Minors will not be approached for assent due to the age group of children included in the trial, however age-and-stage-of-development-appropriate REC-approved Patient information Sheet, describing (in simplified terms) the details of the trial intervention, trial procedures and risks are available.

Child's name, date of birth, NHS/Health & Care (H&C) number, home address including postcode, and parent/primary caregivers telephone number and email address will be recorded on the consent form to allow the central research team at Queen's University Belfast to contact parents/primary caregivers at 12 and 24 month time points for questionnaire completion and interviews. These details will be stored on an access restricted part of the database hosted by LCTC. Health Economics researchers /LCTC will also use this information to gather data from external administrative organisations.

Parents/primary caregivers will also be asked for permission for the CHOICE central research team to write to the Headteacher of the child's school advising that their pupil is taking part in a dental clinical trial, that parental consent has been given for a final dental check-up to be undertaken at the child's school, and that the CHOICE central research team will be in contact to make arrangements convenient to the school for a dental assessor to attend to undertake a dental check-up at school for the child. The name and address of the primary school the child is attending or planning to attend at age 4 years will be collected on the consent form. Permission will also be sought to request information of any new school the child moves to.

Parental/primary caregiver consent will also be sought to follow the participant's dental treatment records both at the practice and if hospital attendance for dental treatment has been made for up to 10 years from the end of study. Parents will be asked if similar dental records can be followed up for any siblings (up to 11 years of age at study entry) of the participant living at the same address and who attend the same dental practice as the participant. Names, date of birth and gender of any siblings will be requested to allow us to do this. Consent will be sought to request NHS/H&C number of siblings from dental practices.

Consent for the ENCOURAGE sub-study will be optional on the main CHOICE consent form. The parental/primary caregiver can choose to consent to the CHOICE trial only without opting to join the ENCOURAGE sub-study.

10.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified and trained Dentist or Dental Therapist of the CHOICE trained staff who are named on the delegation log. This must not occur until fully informed consent is documented and prior to completing baseline assessments and randomisation. Eligibility confirmation must be documented in the participant's dental records and on the trial database. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation).

10.4 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 10.8) in order to accurately complete the Baseline CRF and collect the necessary information for the trial analyses. This includes the following:

- Demographic information
- Socio-economic information
- Dental status (recorded by trained general dental practitioner/dental therapist)
- Oral Health Behaviours and Regret/Relief Questionnaire (completed by parent/primary caregiver)
- Parental-Caregiver Perceptions Questionnaire (completed by parent/primary caregiver)
- EQ-5D-Y Proxy (completed by parent/primary caregiver)

The patient can proceed to randomisation once all baseline assessments have been completed (see Section 10.5 for details). Where possible, to maximise participation in the trial, randomisation will take place at the same appointment as completion of baseline questionnaires and/or the delivery of the DR-BNI while adhering to the consort flow diagram.

Socio-demographic data of the child will be collected by questions to the parent/primary caregiver, namely:
Child's age; child sex; child ethnicity: parent/primary caregiver will be asked to choose child ethnicity using ethnic groups used in the 2021 Census of England and Wales for the 3 English Regions and for Northern Ireland, the ethnic groups used in the 2021 Census in Northern Ireland.

Parents/primary caregivers of school age participants will be asked if their child is eligible for Free School Meals.

10.4.1 Baseline Dental Assessment Training

The baseline dental assessments will be undertaken by clinicians (dentists or dental therapists) who have been trained by the CHOICE trial team. The clinicians will attend a training workshop. This training will follow national guidance for epidemiological surveys of child oral health using the same clinical standards, methods and tools. The training will describe and present the standardised criteria for the detection of dental caries (Pitts et al., 1997), discriminating between grades of carious lesions; types of restorations; applying standardised assessments on reasons for teeth absence. The recording of conditions will follow the national coding.

Clinicians will be trained to distinguish between caries confined to enamel and lesions that have progressed to dentine as defined by the criteria including the requirement to record lesions independent of clinical judgement on need for restoration or other treatment. The training includes discrimination of arrested carious lesions. Interactive discussions will be undertaken to support the identification of children at risk of future dental caries and suitable to join the CHOICE trial.

Whist all clinicians within the site can be involved in screening children as potentially suitable to take part in the CHOICE trial, only clinicians who have been trained in the standardised assessment of dental caries, and are delegated to do so, will undertake the baseline dental assessments.

These assessments will also record the presence of dental plaque on index teeth as described in the national guidance.

The final dental assessments conducted 24 months (+/- 3 months) after randomisation will be conducted using the same epidemiological diagnostic criteria and methods as for the baseline dental assessments.

10.5 Randomisation

10.5.1 Randomisation Process

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive either the CHOICE intervention or control (in a ratio of 1:1). Randomisation should occur no more than 6 weeks following consent and must be once:

a) Fully informed electronic consent/proxy consent has been obtained (and appropriately documented)
b) Eligibility criteria have been fulfilled (and eligibility confirmed)
c) Baseline data collection and assessments have been completed.

A personal login username and password, provided by the LCTC, will be required for REDCap and the randomisation system will be integrated into REDCap..

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

10.5.2 Randomisation System Failure

If there are problems with randomising a participant, please contact the LCTC on 0151 795 5294 or via email at choice.study@liverpool.ac.uk
The coordinating team at the LCTC are available (Monday to Friday between 9:00 to 17:00 excluding bank holidays and University of Liverpool closure days).

10.6 Intervention

A delegated member of the CHOICE site staff must complete the following assessments and record them on the trial database for both child and parent/primary caregiver participants who have received the CHOICE intervention:

- **Participant's (parent/primary caregiver) goals and prescription for change**; recorded as part of the CHOICE intervention
    - These will be entered onto the trial database and transferred securely to the CHOICE Central Research Team at Queen's University Belfast.
- **Timing of the intervention**
    - Once the research team are made aware of the group allocation, participants (parent/primary caregiver) will receive their allocated intervention ideally within 6 weeks of randomisation but no longer than 12 weeks after. This will be administered as described in Section 9.
- **Delivering DR-BNI in a comprehensible way**

- It is recognised that some parents/primary caregivers may need the support of interpreters to ensure that the intervention, DR-BNI, can be received in a comprehensible way. If required, sites should follow standard NHS procedures to book an interpreter to ensure that eligible families are not excluded from participation in the CHOICE trial.

10.7 Final Dental Assessment

Final dental assessments are due 24 months (+/- 3 months) after randomisation. These assessments are made by an examination of the condition of the teeth in a visual check by a trained examiner using standardised criteria. It is a simple check taking 5 to 10 minutes, is non-invasive and undertaken with portable dental equipment of a dental light and sterile disposable mirror, probe and cotton wool rolls to dry the teeth. The procedure is explained to the child and permission sought of the child by the dentist to look at the teeth.

As these are critical assessments for the trial outcome, considerable efforts will be made to maximise the opportunity to see the child, however, a balance must be struck between this aim and being intrusive or burdensome to the family. We will therefore attempt to establish the best location (dental practice or school) in advance of arranging the final dental assessment for each child.

- For the final dental assessment in dental practices, participants will be invited to attend the dental practice for a maximum of three appointments and if taking place in school, they will be invited to have the final dental assessment for a maximum of two appointments.

- A second appointment will be made for those who contact the dental practice to cancel the first appointment (a third appointment can be arranged in exceptional circumstances eg. sickness, and if the family are amenable to this).

- If the participant fails to attend the dental practice or if the participant is no longer known to the practice, the central research team will send a follow-up letter to the Headteacher of the child's school to arrange to undertake the assessment in school.

- A letter will be sent to the participant's home address advising the parent/primary caregiver who gave consent for the final assessments to be conducted in school of the date and time the assessment is planned.

- If the child is absent from school on the booked day, one follow-up time will be arranged and the parent/primary caregiver advised by letter.

- If the child is absent on the second school visit for the 2-year final assessment and the family is not contactable by the central research team, the participant will be considered lost to follow-up

10.8 Schedule for Assessments and Follow-up

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

	Visit

Procedures	Screening/ Baseline*	Randomisation (within 6 weeks of consent)	CHOICE Intervention Visit	ENCOURAGE Sub-study 6 months (+/- 1 month) (optional - must consent)	12 months (+/- 3 months)	24 months (+/- 3 months)	Study Completion
Signed Consent Form (including collection of contact details)[1,2]	X						
Assessment of Eligibility Criteria	X						
Demographic information	X						
Socio-economic data,	X						
Baseline dental assessment (Dentist)[1]	X						
Oral Health Behaviours and Regret/Relief Questionnaire[2]	X**				X	X	
Parental-Caregiver Perceptions Questionnaire[2]	X**				X	X	
EQ-5D-Y Proxy Questionnaire[2]	X**				X	X	
Randomisation		X					
Delivery of CHOICE intervention to child's parent/primary caregiver			X***				
Participants goals and prescription for change[2]			X***				
Audio recordings of CHOICE intervention			X***				
CHOICE intervention feedback and Regret/Relief Surveys[2]			X***				
Qualitative Interviews****					X	X	
Safety data assessment			X		X	X	
Final dental assessment (Blinded Assessor)[1]						X	
Dental treatment and dental pain data recorded from patient records by GDP[1]					X	X	
Dental treatment data requested from NHS[1]							X
ENCOURAGE saliva sample (optional – must consent)		X*****		X*****			

*At baseline, informed consent must be in place prior to any procedures occurring

** The questionnaires at Screening/Baseline may be collected at a subsequent visit where randomisation and the intervention visit occurs as long as they are completed prior to randomisation.

***For those allocated the intervention, this must be completed within 12 weeks of randomisation. These activities can occur on the same day as randomisation

**** Qualitative interviews will be carried out 6-12 months following intervention

[1]Child data collection

[2]Parent/Primary caregiver data collection

***** ENCOURAGE saliva samples will be collected at Randomisation visit and 6 months (+/- 1 month) from randomisation. This is an optional sub-study.

Participant follow-up will occur 12 months (+/- 3 months) and 24 months (+/- 3 months) following randomisation. Parents/primary caregivers of participants assigned to the Intervention Group will have a trial visit to receive the intervention within 6 weeks of randomisation

At 12 months (+/- 3 months) post randomisation, the dental records will be reviewed to complete the following:

- Dental treatment and dental pain data recorded during the last 12 months
- Safety Data Assessment during the last 12 months

At 24 months (+/- 3 months) post randomisation, the dental records will be reviewed to complete the following:

- Dental treatment and dental pain data recorded during the last 12 months.
- Safety Data Assessment during the last 12 months.

Safety data can be collected as part of the study questionnaires.

A dental assessment will also be completed by a blinded assessor at 24 months (+/- 3 months).

10.8.1 Method of Contact

At 12 months (+/- 3 months) and 24 months (+/- 3 months) post randomisation, parents/primary care-givers will be sent a link to complete the study questionnaires required at these time points. If these are not completed, parents/primary caregivers may be contacted by telephone or post to enhance completion. A password protected keeping in touch website developed by Parenting NI will be made available to participants. This will involve comprehensible information about the trial that is publicly available and prompts for continued involvement.

10.8.2 Safeguarding

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

10.8.3 Efficacy Assessments

The primary outcome, the efficacy assessment, is measured 24 months post-randomisation (+/- 3 months), and is the development of caries in any tooth which was caries free or unerupted at baseline. Caries is measured at the dentinal level of involvement (Pitts et al., 1997). Children will be examined supine with a single-use plane mouth mirror, and teeth will be illuminated by a portable Daray light of 2,000 lux. The presence of upper anterior buccal plaque will be recorded as an indicator of oral cleanliness. Teeth will be examined for untreated caries into dentine, restorations, and fissure sealants. (Pitts et al., 1997) Cotton wool rolls will be used to dry teeth, and probes will be available to remove debris and to check the integrity of restorations and the presence of sealants. Examining procedures are those set by the national dental epidemiology programme under which children are examined in school using mobile equipment (Public Health England, 2021) . Assessments will be conducted in the child's dental practice, where possible, or in the child's school or if requested by parent, at the child's home. All dental assessments will be blind to group assignment. Organisation of the timetable for the clinical assessments including contacting practices, schools and families will be undertaken by the CHOICE central research team based at Queen's University Belfast.

All dental treatment that is provided will be recorded by the participants' general dental practitioner (GDP) during the trial period. At the time of final assessment, dental records will be examined of the trial participants by the GDP to capture all the dental treatment and reported dental pain. Hospital records of dental extractions will also be recorded. Where consent has been provided, administrative records will be used for the study period for any siblings (aged up to 11 years on study entry) residing with the participant and attending the same dental practice to assess their dental treatment.

10.8.4 Process Evaluation

Mechanisms of impact will be investigated via qualitative interviews with up to 40 parents/primary caregivers 6-12 months after receiving the CHOICE intervention. An interview schedule will be developed to assess how the

intervention activities and participants' interactions trigger reported change in toothbrushing and sugar behaviours, maintenance of any behaviour change, automaticity, self-efficacy, intrinsic motivation, relief/regret and any unintended effects. Interviews will be conducted online/over the phone and audio-recorded for transcription and subsequent analysis.

Fidelity to the CHOICE intervention will be assessed from audio-recordings routinely undertaken as a part of the delivery of the intervention.

10.8.5 Implementation

Barriers and facilitators to routinely integrating DR-BNI into general dental practice will be explored from the Theoretical Domains Framework (TDF) perspective (Atkins et al., 2017) as well as speaking with the principal investigators at each site (dental practices) to capture usual preventive care for children. This will be undertaken by focus groups/interviews with key PPI stakeholders including parents/primary caregivers and the dental team. An interview schedule for each group will be developed guided by the TDF and data will be analysed using framework analysis (Gale et al., 2013). These will take place between 24-36 months from the start of the trial. Interviews will be conducted online/over the phone and audio-recorded for transcription and subsequent analysis.

10.8.6 Safety Assessments

Active monitoring of safety events experienced by trial participants will take place from randomisation until 24 months (+/- 3 months) post randomisation. Reportable safety events will include:

- A serious adverse event related to the trial procedures or intervention

10.8.7 Quality of Life Assessments

EQ-5D-Y questionnaire will be completed by parent/primary caregiver participants at Baseline, 12 month and 24 month follow-up.

10.8.8 Health Economic Assessments

Utilization of care will be taken from clinical records and monetised using the Northern Ireland Statement of Dental Remuneration for care provided by the GDP and from National Cost Collections for hospital provided extractions. These costs will be aggregated over the 24-month study period in the base case analysis (and over 10 years in the follow-up study). To these will be added the cost of the intervention for the intervention group. Intervention costs will be based on nurse delivery time as recorded by the providing nurse and monetised using agenda for change pay rates for a dental nurse at band 2 in the base case analysis. As a validation exercise a random sample of intervention delivery times will be timed by the research team and compared with those reported by nurse providers. Incremental costs in the base case analysis will be based on differences in costs over 24 months between the control and intervention group. As a range of outcomes are captured in the study including the proportion who accumulate additional caries, the number of fillings provided, episodes of pain and quality of life (QOL) measures, a range of incremental effects will also be calculated based on differences in these at 24 months. Where appropriate, for example in respect of quality of life, incremental effects will be based on differences in the change in QOL between baseline and follow-up between intervention and control groups.

Mean differences in cumulative discounted costs and effects between the intervention and control groups will be described and tested using standard parametric approaches to examine differences in mean costs, proportion of children whose caries progress, episodes of pain, fillings and health-related quality of life etc. A series of incremental

cost effectiveness ratios will be estimated detailing the difference in cost divided by the difference in effect between intervention and control groups. To take account of the possibility that costs, and effects are jointly distributed, uncertainty around ICERs will be explored in deterministic models using a nonparametric bootstrapping approach and uncertainty around the willingness to pay for outcomes using cost effectiveness acceptability curves.

A discount rate of 1.5% will be used in the base case analysis based on the intervention being construed to be a public health intervention. Missing data will be imputed using multiple imputation methods. An intention to treat approach will be adopted for analyses. Given observed disparities in oral health and use of dental services related to socio-economic status (SES) we plan to undertake sub-group analysis related to socio-economic status and ethnicity. Should significant differences in cost-effectiveness exist, the samples will be re-weighted to adjust for differences in SES and incremental cost-effectiveness re-estimated. As an additional check, a seemingly unrelated regression approach will be used to estimate ICERs and models adjusted and unadjusted for SES reported. This approach will be repeated with respect to ethnicity.

A series of sensitivity analyses will be undertaken. Individual parameter values will be varied in a series on one way sensitivity analyses that include unit costs, discount rates and time taken to deliver the intervention. Spill-over effects related to sibling effects will be added to those experienced by the index based on observed differences in use of dental care and the relationships between use of dental care and QOL observed from the literature and observed in the study. (How for example QOL varies with additional fillings and extractions,) A probabilistic sensitivity analysis will be used to examine the sensitivity of results to joint variations in input parameters.

10.9 Intervention Discontinuation and Participant Discontinuation/Withdrawal

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

10.9.1 Premature Discontinuation of Trial Intervention

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

- Participant-led i.e., request by the participant or parent/caregiver
- Insufficient time to complete the intervention

    - Discontinuation from trial intervention does not mean discontinuation of the trial altogether, and the remaining trial procedures, follow up assessment and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn, see section 10.9.3). Intervention withdrawal should be recorded on the trial database.

10.9.2 Participant Withdrawal

Persons with parental responsibility are free to withdraw consent for them/their child at any time without providing a reason. If consent is withdrawn for the trial, data will be collected up to the point of that withdrawal of consent and included in the analyses. The participant will not contribute further data to the trial and the Withdrawal eCRF should be completed.

If a participant withdraws from the ENCOURAGE sub study or the CHOICE study then no further saliva samples will be collected. If any samples have already been collected, the samples will continue to be stored. Should a participant wish for a sample to be destroyed then they can request this and this will be made clear in the Patient Information Sheet.

Any SAEs will be notifiable to the LCTC via processes detailed in Section 12 even if a participant has withdrawn from follow up.

10.9.3 **Loss to Follow-up**

A participant will be considered lost to follow up if they fail to attend the final dental assessment as discussed in section 10.7.

Contact details (telephone number and/or email address and/or postal address) will be collected at the baseline visit, and entered into a restricted-access area of the trial database to allow telephone follow-ups to occur.

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

Data collection with NHS Digital, NHS BSA, BSO and PAS will continue, if consented at baseline, unless the participant confirms that they would like to withdraw consent.

10.10 **End of Trial**

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

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

10.10.1 **Study Discontinuation**

In the event that the study is discontinued, there are no considerations for continuation of allocated treatment as this occurs only once following randomisation.

11 SUB-STUDIES/NESTED STUDIES

11.1 Study Within A Trial (SWAT)

11.1.1 Rationale

Achieving recruitment targets and widening access for all eligible participants is a common challenge in dental clinical trials (Robinson et al., 2016). Therefore, we plan to put in place additional measures (Motivational Letter vs Motivational Letter and Family Oral Health Toolkit) from the outset of the recruitment to the CHOICE trial and we will evaluate the value of these measures alongside the trial..

Widespread and effective long-term screening of children's oral health in school is not undertaken in England and Northern Ireland (Arora et al., 2019, Milsom et al., 2006). In England, biennial surveys of the dental health of 5-year-olds are conducted to a national protocol and co-ordinated by Public Health England. From 1985-2007, these surveys were conducted under a nationally co-ordinated programme in which children were examined under a passive consent process, that is, an information letter was sent to parents advising of the survey with the ability to withdraw their child, but explicit parental consent was not sought. During these times, participation rates were 75% and above. From 2007/08, guidance from the Department of Health changed to a requirement for positive parental consent for dental surveys (Davies et al., 2011).

The process of recruitment to screening of children's oral health has been unchanged and remains to be by letter to parents through schools, with one reminder advised. To undertake the dental examination, a signed return is required from parents. The percentages of parents of 5-year-olds consenting and whose children received dental examinations for the National Dental Epidemiology Programme in 2017 were: Essex 52%; Liverpool 51% and Leeds 56%. Only 6% of parents declined to participate, and absenteeism on the day of examination was low at 3%; the most common reason for non-participation was non-response (32%;) (Public Health England, 2017). When this change to parental consent was introduced, studies were conducted to compare strategies for maximising consent rates for these dental surveys but found no differences and concluded that further research was needed (Glenny et al., 2013). A range of strategies had been identified through study and review, namely: greater promotion of the surveys to school heads, teachers, parents and pupils; having reminder contacts; and having a member of the survey team co-ordinate and closely monitor the recruitment process (Robinson et al., 2016).

Taking the above into account, recruitment of the target population to clinical trials is particularly challenging especially when reaching diverse communities. A systematic review of studies exploring recruitment and retention to RCTs involving children identified several barriers (Robinson et al., 2016). These included younger parents, those from a low SES and ethnic minority background as well as those who had completed less education. While the systematic review did not find consensus across studies meaning that these characteristics do not necessarily predict recruitment and retention into RCTs, they did recommend exploring the process of participation for such families. We recognise the challenges to recruitment to the trial such that many children who develop dental caries have sporadic attendance at dental practice and often only attend when acute problems arise resulting in limited treatment options.

11.1.2 Brief Motivational Interventions to Promote Health Behaviour

Health behaviour theories are frequently used to design brief psychological interventions to promote positive health behaviour change or to motivate patients to attend a health care service, because interventions based on a theoretical framework are considered most effective (Michie et al., 2008). Volitional help sheets draw on the transtheoretical model of change (Prochaska and DiClemente, 1983) to provide a means by which individuals can generate their own behaviour implementation intentions to help them move from inaction to action. Provision of a volitional help sheet has been found to successfully reduce cigarette smoking (Armitage, 2008), alcohol consumption (Armitage and Arden, 2012), and suicidal ideation and behaviour (Armitage et al., 2016, O'Connor et al., 2017).

Motivational letters guided by principles of Motivational Interviewing (Rollnick and Miller, 1995, Miller and Rollnick, 2012) have been found to successfully promote a range of health-related behaviours including attendance to psychological treatment for gambling disorder (Pfund et al., 2020), cardiac rehabilitation enrolment and attendance (Pfund et al., 2020, Mosleh et al., 2014, Wyer et al., 2001), and cancer screening uptake (Chan and So, 2021). They are often used because they are considered low-risk and require lower amounts of time, effort, and money to deliver, while providing the potential for considerable health gains (Dressler et al., 2012).

A study exploring how concepts from the Theory of Planned Behaviour (TPB) (Ajzen, 2011) are operationalised in the design of motivational letters of invitation to cardiac rehabilitation highlighted the importance of relatable and personal messaging, and the use of the future tense in sentences to motivate patients to engage in future behaviour (Dressler, 2018). The findings were related to the subjective norm, perceived control, and attitude components of the TPB, which together are involved in the process from intention to behaviour. Firstly, both letters reviewed in the study were related to subjective norm component by writing about what the doctor or other health care professional expected of patients regarding cardiac rehabilitation. Secondly, perceived control was reflected in the provision of information about what cardiac rehabilitation is. Finally, attitude was operationalised through language that conveyed a positive outlook, emphasised the importance of engaging in the target behaviour, and explicitly stated how negative consequences of not engaging in the target behaviour can be avoided.

When designing interventions to promote behaviour change, it is important to specify the target behaviour to be changed and to identify what needs to change in the person and/or the environment to achieve the desired behaviour change. The COM-B model proposes that for any behaviour to occur, the person must have the capability to perform the behaviour (e.g., strengths, knowledge, skills), there must be the opportunity for the behaviour to occur (i.e., accessibility, affordability, social acceptability, time), and there must be sufficient motivation to either do the behaviour or not to engage in a competing behaviour (Michie et al., 2014). Therefore, the content in the motivational letter used in the present study will seek to promote the key areas of participants' capability, opportunity, and motivation.

Children's stories can be effective as oral health promotion interventions. O'Malley and colleagues developed a storybook intervention called 'Kitten's First Tooth' (KFT) using established behaviour change techniques (O'Malley et al., 2017). The intervention was effective in increasing parental self-efficacy and parent intention for their child to attend the dentist. The present study will use the KFT storybook as part of a family oral health toolkit (including information on how to access an audio version of KFT online, toothbrush, and toothpaste) in addition to a motivational letter to promote attendance to a dental check-up in irregular dental-attending children while also providing an opportunity to enhance recruitment to the CHOICE Trial.

11.1.3 **Methodology**

11.1.3.1 Aims and Objectives

The CHOICE Trial will enhance its recruitment strategy from the outset to include a motivational letter and family oral health toolkit to promote engagement of harder to reach families (i.e., those who are none or irregular dental attenders) via a primary school and nursery school outreach programme for children aged 4 to 7 years, that is, children attending nursery and primary school; initiated by dental nurses from the CHOICE general dental practices during the first 18 months of recruitment.

The research questions are,

1. Does a motivational letter and oral health toolkit intervention enhance recruitment to the CHOICE Trial in irregular dental-attending children?
2. What are the facilitators and barriers to recruitment of the target population?

11.1.3.2 Participants

Participants will be parent's/primary caregivers and their child aged 4 to 7 years of age attending nursery or primary school in four regions of the U.K. who self-identify as not currently having a dentist for their child. (The North West of England; East of England; Yorkshire and the Humber; Northern Ireland). This will be established by sending a motivational letter home from school providing information on how to get registered with a local CHOICE dental practice if their child does not currently have one. Approximately half of the schools will receive intervention 1, and half will receive intervention 2 (based on recruitment targets). The recruitment strategy will involve dental nurses engaging with around 36 schools within the catchment area of 18 CHOICE dental practices who agree to take part in the SWAT. Given the goal here is to identify children who don't currently have a dentist and enhance recruitment of them to the CHOICE trial, no specific sample size is calculated.

11.1.3.3 Design

- INTERVENTION 1: Parent's/primary caregivers of potential participants will be sent a motivational letter and a voucher for a family oral health toolkit (containing Kitten's First tooth storybook, toothbrush, toothpaste) to be redeemed at the first dental visit for each child. This will be delivered to home via school with the motivational letter for parents/primary caregiver encouraging a visit for a dental check-up.
- INTERVENTION 2: Parent's/primary caregivers of potential participants will be sent a motivational letter to encourage attendance for a dental check-up.

11.1.3.4 Procedure

For research question 1: the 18 CHOICE dental practices across each of the four regions will engage with two local nursery/primary schools within the local area. Potential participants in one of the schools will receive the motivational letter and a voucher for a family oral health toolkit, and those in another school will receive only the motivational letter. Potential eligible participants will be invited to participate in the CHOICE trial in addition to receiving routine dental care. Those in receipt of the oral health toolkit voucher at the dental appointment can exchange the voucher for the free oral health toolkit, which will be recorded by the dental practices. All quantitative data will be anonymised and collected by the dental practices then sent to the LCTC for analysis.

For research question 2: parents/primary caregivers who consent to take part in an interview will be asked about the things that helped them decide whether to take part in the CHOICE trial. Participants will be invited to attend a short online focus group with other primary caregivers of 3–7-year-old children who were invited to participate. The interview will be developed using the Behaviour Change Wheel (COM-B). The interview will explore participants' capability, opportunity, and motivation, to engage in the target behaviour of dental check-up attendance and agreement to enter the CHOICE Trial.

11.1.3.5 Motivational Letter and Family Oral Health Toolkit

The one-page motivational letter will be developed using the Behaviour Change Wheel (Michie et al., 2011) and will promote participants' capability, opportunity, and motivation, to engage in the target behaviour of dental check-up attendance and agreement to enter the CHOICE Trial.

The redeemable voucher can be exchanged for a Family Oral Health Toolkit, consisting of a physical copy of, and weblink to, the Kitten's First Tooth video storybook (O'Malley et al., 2017) and a toothbrush and toothpaste.

11.1.3.6 Analysis

Primary analysis will be a comparison of attendance for a dental check-up and consent/recruitment into the CHOICE Trial. The following outcome measures will be assessed, grouped by intervention:

a) Response rate of attendance for a dental check-up in potential participants who are none or irregular attenders.

b) Proportion of potential participants who consent to take part and are recruited into the CHOICE trial.

In addition, the interviews will be analysed using Reflexive Thematic Analysis (Braun and Clarke., 2019).

11.2 ENCOURAGE sub-study

11.2.1 Rationale:

The ENCOURAGE sub-study is an EME Mechanistic study embedded into CHOICE It is funded by the NIHR EME programme (NIHR151317). Encourage will investigate the biological mechanism of the DR-BNI intervention in CHOICE. There is strong evidence that twice-daily tooth brushing with a fluoride toothpaste is effective in the prevention of

childhood caries (Mejàre et al., 2015). Tooth brushing also aids removal of dental plaque bacteria and facilitates removal of foodstuffs (sugars) that adhere to the teeth where they can be metabolised to acids by plaque bacteria. Effective twice-daily tooth brushing with fluoride toothpaste supports maintenance of the oral microbiome in a beneficial (eubiotic) state (Twetman, 2018). However, families, especially those from poorer socio-economic backgrounds, who face many life challenges, struggle to prioritise oral hygiene over other more pressing needs.

Understanding the biological mechanism of action of the DR-BNI would facilitate objective monitoring of adherence to caries prevention goals (sugar control, oral hygiene). In turn this would obviate the need for unreliable food diaries and may predict future caries at a much earlier stage than waiting for new carious lesions to appear. Caries is a lengthy process in which the tooth enamel and then the underlying dentine is demineralised by acids produced by fermentation of dietary sugars by plaque bacteria. Caries is often associated exclusively with the carious lesion or cavity. However, the caries process is more accurately described as a continuum of many cycles of tooth demineralisation and remineralisation. Demineralisation begins at the atomic level at the crystal surface inside the enamel or dentine and can continue, unless halted, until a cavity is formed (Featherstone, 2008). During the early stages of caries development the process of demineralisation could be halted and remineralisation encouraged, if the causative factors (mainly acids produced from fermentation of sugars by oral bacteria) are brought under control via appropriate preventive measures. There are many possibilities to intervene in this continuing process to arrest or reverse the progress of the carious lesion. One possibility is behavioural intervention, such as the DR-BNI (targeting sugar intake and improving oral hygiene), which was previously shown to be successful and ENCOURAGE will develop an understanding of the mechanism of DR-BNI, to support adherence monitoring and/or caries prediction strategies.

Production of acids by oral bacteria is the main cause of enamel demineralisation and initiation of the caries process. Many organic acids are produced in this process, with lactic acid being one of the principal acids produced by oral bacteria following sugar intake, and which has been shown to correlate with caries (Gao et al., 2001; Minah & Loesche, 1997; Margolis & Moreno 1994; . Production of lactic acid requires both the presence of dental plaque (bacteria) and dietary carbohydrates in the form of sugars (source of carbon for bacterial fermentation). Lactic acid levels in saliva could therefore represent an independent surrogate for adherence to both tooth brushing (which influences abundance of plaque bacteria) and dietary sugar control (which influences amount of sugar available for bacterial fermentation).

The saliva samples will be collected at baseline (randomisation visit) and then at 6 months (+/- one month) after randomisation for both groups. Previous research has confirmed that the median timeframe for habit formation is 66 days (Lally et al., 2010). There is however likely to be fluctuation in this and there needs to be additional time allowed for behaviour changes to be embedded into daily routines, as we understand that it takes time and practice to reinforce caries prevention behaviours. Embedding these behaviours may take 2-3 months and some families may delay the start of behaviour change; by 6 months post-intervention those that are changing will have done so.

Preventing caries developing depends on consistent adoption of healthy behaviours of brushing twice daily with fluoride toothpaste and restricting sugars intake. It is these behaviours that are set as goals by parents through the intervention DR-BNI.

11.2.2 Hypothesis: Changes in diet (reduction in sugar consumption) and/or improved oral hygiene (tooth brushing with fluoride toothpaste twice daily and reducing dental plaque) as a result of DR-BNI behavioural intervention, may result in reduced salivary lactic acid levels. The mechanistic hypothesis is that adherence to caries prevention goals will reduce lactic acid levels in saliva by 6 months post intervention, which will then contribute towards protection against the development of caries over the two years post-intervention.

11.2.3 Aims and objectives

The **aim** of this research is to determine if changes in salivary acid levels and changes in the oral microbiome have a role in the mechanism of action of the DR-BNI behavioural intervention in preventing child tooth decay.

Primary objective: To quantify salivary levels of lactic acid at baseline, and at 6 months follow-up, and determine if change in lactic acid concentration contributes towards the effect of intervention versus control on the caries outcome at 2 years.

Secondary objectives:
(a) To quantify salivary levels of pyruvic acid, citric acid, 2-ketoglutamic acid, succinic acid, malic acid and fumaric acid at baseline, and at 6 months follow up, and determine if changes in these levels contribute towards the effect of intervention versus control on the caries outcome at 2 years.

(b) To determine if salivary acid levels correspond with microbiome eubiosis or dysbiosis by studying the oral bacterial microbiome and fungal mycobiome in a subset of 60 children at baseline, and at 6 months follow up.

11.2.4 Sample collection handling and storage:
Saliva samples will be obtained from 400 children at baseline (randomisation visit), and at 6 months (+/- 1 month) following randomisation. Saliva will be collected for approximately 5 minutes and will represent pooled salivary gland secretions, containing salivary metabolites, as well as reflecting the bacterial microbiome and fungal mycobiome. Saliva collection is a simple procedure, considered to be non-invasive. A standard operating procedure (SOP) will be developed for saliva collection, and dental nurses will be trained in saliva collection from children. Children unable to produce saliva over a 5 minute period will be excluded from the study.

Saliva samples will be frozen immediately at -20ºC in small freezers. The samples will be dispatched via courier to local University freezers, regularly for storage at -80ºC. Samples will subsequently be stored in line with Human Tissue Act guidelines in University freezers at -80ºC until required for analysis.

11.2.5 Sample analysis
A full audit of saliva samples will be undertaken and the samples will be prepared for metabolomics and microbiome analysis. Following laboratory analysis, the metabolomics and microbiome data will be interpreted and the linkage of the large laboratory dataset with the outcomes of CHOICE will occur.

(i) Metabolomics: Saliva samples will be analysed by a targeted metabolomics approach by Metabolon. The dataset produced by Metabolon will be analysed in line with the microbiome data (below).

(ii) Bacterial microbiome and fungal mycobiome: Saliva samples will subsequently be analysed for their bacterial microbiome and fungal mycobiome. The DNA will be extracted from saliva in preparation of next generation sequencing. We have previous experience of microbiome analysis from clinical samples and significant expertise will be required in microbiome data analysis to interpret the raw, next generation sequencing data. The microbiome data will be analysed alongside the metabolomics data.

Statistical analysis
The primary analysis will be a mediation analysis using Baron & Kenny's method to test for partial mediation with a series of regression analyses. We will conclude that mediation is present if the four statements below are true:

1. The total of effect of DR-BNI on caries is significant
2. The effect of DR-BNI on lactic acid is significant
3. The effect of lactic acid on caries, adjusted for DR-BNI is significant
4. The direct of effect of DR-BNI on caries adjusted for lactic acid is reduced from the effect modelled in step 1.

The primary objective is to quantify salivary levels of lactic acid at baseline, and at 6 months follow-up, and determine if change in lactic acid concentration contributes towards the effect of intervention versus control on the caries outcome at 2 years.

The secondary objective are to
(a) To quantify salivary levels of pyruvic acid, citric acid, 2-ketoglutamic acid, succinic acid, malic acid and fumaric acid at baseline, and at 6 months follow up, and determine if changes in these levels contribute towards the effect of intervention versus control on the caries outcome at 2 years.

(b) To determine if salivary acid levels correspond with microbiome eubiosis or dysbiosis by studying the oral bacterial microbiome and fungal mycobiome in a subset of 60 children at baseline, and at 6 months follow up.

12 SAFETY REPORTING

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

12.1 Terms and Definitions

12.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the intervention under investigation.

12.1.2 Related Adverse Event (Related AE)

An AE which resulted from administration of any of the research procedures – i.e. assessed as "probably", "possibly" or "almost certainly" related to the trial procedures.

12.1.3 Related Unexpected Adverse Event (RUAE)

A Related AE which is not expected, i.e. not consistent with the known effects of the trial procedures.

12.1.4 Serious Adverse Event (SAE)

An adverse event which meets the definition of "serious".

12.1.5 Related Serious Adverse Event (Related SAE)

A SAE which is assessed to be "probably", "possibly" or "almost certainly" related to the trial procedures.

12.1.6 Related Unexpected Serious Adverse Event (RUSAE)

A Related SAE which is not expected, i.e. not consistent with the known effects of the trial procedures.

12.2 Assessment of Seriousness

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

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

- Results in death;
- Is life-threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation);

- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of trial participants, or their partners, regardless of time of diagnosis), or
- Is otherwise considered medically significant by the investigator.

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

12.3 Severity of Adverse Events

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

12.3.1 Table 1: Severity Grading

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

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 12.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

12.4 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assessment of relationship of adverse events to the intervention is a clinical decision based on all the available information at the time of the event. The assignment of the causality should be made by a suitably qualified and delegated Dentist (Investigator) responsible for the care of the participant using the definitions in the table below:

Table 2: Definitions of Causality

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

Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

In the case of discrepant views on causality between the dentist and others, the opinion of the dentist will never be downgraded and the REC will be informed of both points of view.
For the CHOICE trial, only events that are classed as serious and possibly, probably or almost certainly related will be reported by participating site.

12.5 Assessment of "Expectedness"

It is not a regulatory requirement for a reporting dentist to provide their opinion of expectedness. Therefore, the reporting physician at the trial sites will not be asked to make the assessment of expectedness. The assessment of expectedness will be made by the Chief Investigator.

An event will be considered **unexpected** if it is not listed within the current and approved protocol (see Table 2: Expected Events) for the study at the time of the event's onset. This includes events that are more frequently reported or more severe than previously reported.

A serious adverse event whose causal relationship to the intervention is assessed by the dentist/delegated other as "possibly", "probably", or "almost certainly" is considered to be a related SAE. If this is then classified by the CI or delegated other as unexpected then this event should be reported as a RUSAE.

12.5.1 Table 2: Expected Events

Event
Distress from parent/primary caregiver when discussing their child's oral health

12.6 Time Period for Active Monitoring of Safety Events

All related SAEs should be followed up until satisfactory resolution or until the dentist responsible for the care of the participant deems the event to be chronic or the patient to be stable. Active monitoring of safety events experienced by trial participants will be from the period of randomisation, until the patient has had their final 24 month examination.

12.7 Notes on Safety Event Recording

Due to the low-risk nature of the trial and the type of intervention, adverse events are not expected and do not need to be reported. Only adverse events that are deemed serious and possibly, probably and almost certainly related are to be reported to the LCTC. The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

12.8 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the database **within 24 hours** of becoming aware, preventing any further contact with the bereaved family.

12.9 Reporting Procedures

Due to the nature of the trial and the intervention, adverse events will not routinely be reported. The occurrence of a safety event that is serious and related may come to the attention of research staff during routine study visits, from the participant's notes, directly from the participant or by other means. Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given in section 12.10 below to aid in determining reporting procedures for different types of adverse events.

12.9.1 Related Serious Adverse Events

Related SAEs should be reported to the LCTC within 24 hours of the local site becoming aware of the event using the SAE eCRF form. The SAE form asks for the nature of the event, date of onset, severity, corrective therapies given, outcome and causality. The reporting dentist should assign the causality of the event. Additional information should be provided within 5 days if the event has not resolved at the time of reporting. As a minimum, the SAE form should contain the following information:

Minimum information required from site	Corresponding data/information
Valid registration number and Sponsor study number	ISRCTN number and sponsor study number
One identifiable coded subject	Patient study number
One identifiable reported	Study site number
	Reporting site research team member (PI/delegate)
One related serious safety event	Description of the event, including date of onset
	The reason why the event is classed as serious
One suspect intervention	The **CHOICE** intervention
A causality assessment	Investigator assessment of causality

Once reported to the LCTC, the CI (or delegated other) will be asked to review the event and provide their opinion on expectedness. Any Related and Unexpected Serious Adverse Events (RUSAEs) must be emailed to the REC by LCTC using the HRA non-CTIMP safety report to REC form. These must be sent within 15 days of LCTC becoming aware of the event. All dentists will be informed of all RUSAEs occurring throughout the trial. Local dentists should report any RUSAEs as required locally.

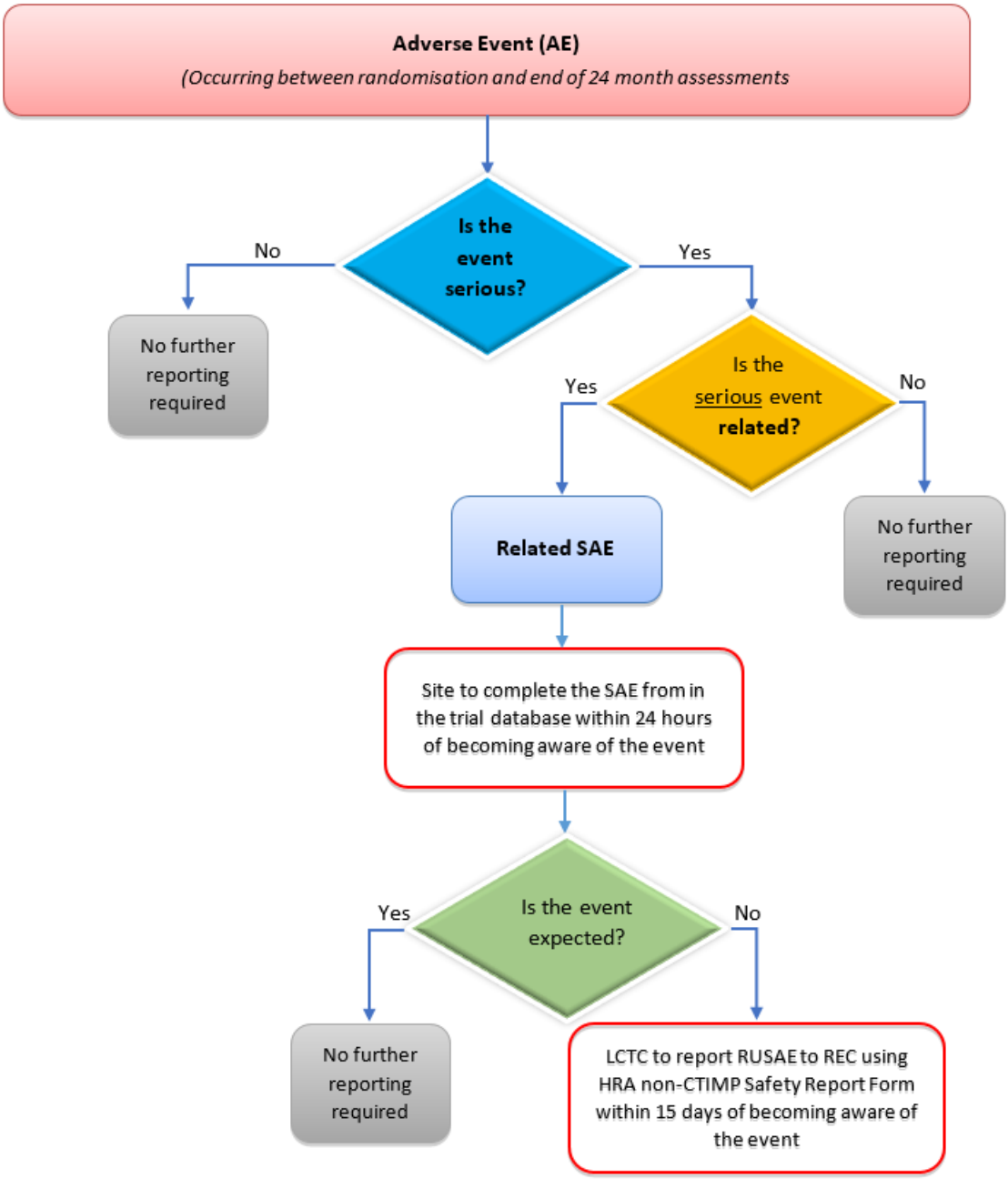
When reporting related SAEs, the reporting dentist should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

12.9.2 Follow up of related Serious Adverse Events

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

- Follow up must continue until clinical recovery is complete or until the event has stabilised. **N.B**. Follow up may continue after completion of protocol treatment if necessary.
- Follow up information is to be entered on to the SAE eCRF
- The appropriate box on the SAE eCRF must be ticked to identify the type of report; this is dependent on the resolution status of the SAE e.g. follow up/final.

12.10 Flowchart for Site Reporting Requirements of Adverse Events



12.11 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events the correct medical terminology **must** be used.

Safety events which meet the definition of "serious" and related (possibly, probably or almost certainly) must be reported in more detail to the LCTC on the SAE eCRF form and must be reported **immediately and in no circumstances later than 24 hours from becoming aware** where they will be appropriately processed.

The SAE eCRF form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified and delegated person/dentist. Minimum reporting information must be provided in initial reports for all studies (see section 12.9.1).

Safety events should be reported by the site in accordance with local policy.

12.11.1 Reporting an initial or follow-up SAE

The Investigator should ensure the actions below are completed for all reportable SAEs:

1) The related SAE should be entered on to the SAE eCRF form on the trial database within 24 hours of becoming aware of the event.

2) When submitting a SAE to the LCTC, the reporter should also telephone the LCTC to advise that a SAE report has been submitted as soon as possible.

3) The responsible investigator must notify their Practice Manager of the event (as per standard local governance procedures).

4) The patient must be identified by trial number, age at time of onset and initials **only**. The patient's name **should not** be used on any correspondence.

5) SAEs must be subsequently followed up in line with the processes documented in section 12.9.2.

12.11.2 Backup SAE reporting

In the event of a problem with the trial database (power failure, server failure etc), a backup SAE form will be made available.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

12.12 LCTC Responsibilities

The trial Sponsor, Queen's University Belfast, have delegated to LCTC the duty of onward reporting of safety events to REC. SOPs will be followed to ensure appropriate reporting as detailed below.

All related "serious" adverse events will be forwarded to the Chief Investigator (or delegated other) by LCTC within 24 hours of receiving the minimum information from site. The CI (or delegated other) will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness".

Safety events which are assessed as "serious", "related" and "unexpected" (i.e. RUSAEs), will be onward reported by LCTC to the ethics committee **within 15 days** of the LCTC first becoming aware of the event.

Additionally, RUSAEs will be reported to the trial Sponsor(s) and Principal Investigators of participating sites.

A list of all safety events recorded for the trial will also be reported annually by LCTC to the ethics committee and Independent Data Safety & Monitoring Committee.

Any concerns raised by the TSC/IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported related SAEs. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

12.12.1 Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of safety events including reporting rates and safety events by site. The LCTC will send Annual Progress Reports (APRs) containing a list of all reported RUSAEs to the main REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

12.12.2 Urgent Safety Measures (USMs)

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

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

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

12.13 Contact Details and Out-of-hours Medical Cover

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

13 STATISTICAL CONSIDERATIONS

13.1 Introduction

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

13.2 Sample Size

13.2.1 Sample Size Calculation

In the clinical trial evaluating the DR-BNI technology in secondary care, the Dental RECUR trial, 62% of children in the control group developed new caries, compared to 44% in the test group, a difference of 18 percentage points. An inclusion criterion for that trial was that the child was scheduled to have at least one primary tooth extracted. The children in the sample achieved had a median of 5 teeth extracted. In addition to the high levels of dental caries experience, the children were aged between 5 and 7 years at recruitment. The children eligible to join the CHOICE trial will have at least one decayed tooth but we will exclude those whose disease is so advanced that they require dental extractions. This is a critical distinction, as one of the objectives of the CHOICE trial is to determine whether earlier intervention in the disease process using DR-BNI can reduce the number of children needing dental extractions; as well as reduce the number having restorations for caries, so further reducing the cost of care to the NHS. The CHOICE trial will also include children at a younger age, from 3 to 7 years, rather than from 5 to 7 years. Therefore, there is potential for a smaller difference to be clinically important achieving a longer-term benefit. These differences in the sample composition mean that it is important to power the trial to detect a smaller difference than found in the RECUR trial, as this difference will be clinically important. Therefore, the CHOICE trial has been powered to detect a clinically significant difference of 12 percentage points.

To give 90% power, with α=0.05, requires 363 participants per group. Allowing for 20% loss to follow-up, we will aim to recruit 454 participants per group, 908 in total. We will provide each of the 4 regions with a recruitment target of 227. Each region aims to recruit 10 dental practices, resulting in an achieved sample size target per practice of 22-23 patients over an 18-month recruitment period.

13.2.2 Feasibility of Sample Size

Included in the Site Suitability Assessment Form to be completed by each dental practice wishing to become a site for the CHOICE trial, the lead practitioner is asked to estimate the number of children seen who could meet the eligibility criteria. Only those practices that see sufficient child patients will be deemed suitable. Therefore, feasibility to recruitment will be considered from the outset.

It is recognised that patient profiles attending the sites do not directly equate with recruitment and the research team has already recognised the challenge of recruitment of suitable patients in primary dental care, as those children with dental disease are more likely to be irregular attenders. Therefore, a study within a trial (SWAT) is planned to support recruitment as described in Section 11. In addition, review of the literature has shown that close monitoring of accruals can help identify recruitment challenges early. Further, in this study, a regional dental lead is a member of the research team in each part of the UK participating. The four regional dental leads will support sites in getting recruitment moving forward and help identify challenges. These aspects will be discussed at Trial Management Group meetings to identify if there are common issues which could benefit from a simple protocol amendment to support recruitment.

Planned recruitment strategies include the delivery of a motivational letter and oral health toolkit intervention to promote the trial amongst irregular-attending children (as part of the SWAT) and the provision of recruitment posters to the CHOICE dental practices.

Retention strategies include the development of an online 'Parent Hub' where participants can receive updates about the progress of the trial and reminders for follow-up visits. In addition, multiple methods for contacting participants will be collected, including postal and email addresses and telephone numbers.

13.3 Method of Randomisation

13.3.1 Allocation Sequence Generation

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

13.3.2 Concealment and Implementation of Allocation Sequence

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

13.4 Blinding Considerations

The assessors collecting outcomes at 24 months will be blinded to treatment allocation. If accidental unblinding occurs, this will be reported to the LCTC. Trial teams at the dental practice and participants will not be blinded.

13.5 Interim Analyses

Analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an IDSMC. These analyses will be performed at the LCTC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

The first six months of recruitment will form an internal pilot, with prespecified progression criteria, which will be reviewed by the IDSMC and TSC. The criteria are based on trial recruitment and receipt of the intervention, and the progression criteria are shown in the table below.

	Red	Amber	Green
Percentage of participants randomised to the intervention group who received the intervention	<90%	≥90%	100%
Recruitment rate/site/month	<70% of target	≥70% of target	≥100% of target
Number of sites opened	<70% of target	≥70% of target	≥100% of target

If the criteria meet the green threshold, recruitment will continue. If they fall into amber, we will consider strategies to improve rates. If they are red, then the possibility of ending the trial early will be discussed with the funders and oversight committees.

13.6 Analysis Plan

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

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

The primary outcome will be compared between groups using logistic regression, adjusted for site and baseline dental caries.

Count outcomes such as number of teeth developing caries, number of fillings and number of extractions will be compared using Poisson regression adjusted for site and baseline caries. Secondary parent reported outcomes will be analysed using linear or logistic regression, adjusted for site and baseline values.

The comparative outcomes in different ethnic groups will be explored by adding terms for ethnicity and interaction terms between ethnicity and treatment to the models of caries and oral health behaviour outcomes. This will be an exploratory analysis as we have not powered the trial to detect interactions.

An exploratory analysis will be carried out to investigate the potential mediating effects of parental self-efficacy and relief/regret on the effect of the intervention on the clinical outcome. This analysis will test for partial mediation using a series of regression analyses. We will conclude that mediation is present if the four statements below are true:

1. The total of effect of DR-BNI on caries is significant
2. The effect of DR-BNI on the mediating variable is significant
3. The effect of the mediating variable on caries, adjusted for DR-BNI is significant
4. The direct of effect of DR-BNI on caries adjusted for the mediating variable is reduced from the effect modelled in step 1.

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

In the treatment arm of the study, for each of the target behaviours (tooth brushing, and reducing sugary foods and drinks) exploratory analyses will be carried out to investigate the potential mediating effects of behavioural intention on the effect of both anticipated and experienced emotions on caries. These analyses will test for partial mediation using a series of regression analyses. If these analyses indicate an association between either of the experienced emotions (regret or relief) and clinical outcome, we will conduct further exploratory mediation analyses to determine whether any association is mediated by the anticipation of the same emotion i.e., whether an association between experienced relief and clinical outcome is mediated by anticipated relief, and whether an association between experienced regret and clinical outcome is mediated by anticipated regret.

13.7 Health Economic Analysis Plan

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

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

Resource related to dental treatments will be taken from routine administrative claims data for the 24 months of the trial and subsequently for the 10 year follow-up. Treatments will be measured and monetised using the statement of dental remuneration for those delivered in the community and standard references for those delivered in secondary care. Where missing data exists multiple imputation methods will be used to estimate missing values. Intervention costs will be added to treatment costs for the intervention group.

Resource use and costs will be reported for the intervention and control groups at 24 months and 10 years using mean, median and standard deviations. Outcomes will be similarly reported at 24 months and for selected outcomes at 10 years. Differences in mean cost and outcomes between groups will be estimated and reported using t-tests. Differences in cumulative care costs over 24 months will be related to differences in effects as cost-effectiveness ratios following a bootstrapping exercise to take account of potential joint distributions between costs and outcomes. Sub-group analysis related to socio-economic status and ethnicity will be explored based on partitioned samples. Seemingly unrelated regression analyses will be used as an adjunct to the bootstrapping exercise and covariates for socio-economic status and ethnicity entered as covariates.

Sensitivity analysis, to include variation in specific elements of cost – for example based on the time and motion study of intervention delivery time – will be undertaken as will a probabilistic sensitivity analysis.

To take account of potential spill-overs related to sibling use of services, routine administrative data on dental service use by siblings aged <11 at the time of the study child's recruitment will be secured. Their use of services will be used to estimate spill-over costs and their outcomes measured or where unobserved estimated based on relationships between costs and outcomes for study children. Spill-over costs and outcomes will be added to those of the study child in sensitivity analysis at 24 months and 10 years.

Cost-effectiveness acceptability curves will be used to assess the value of the intervention assuming a variety of societal willingness to pay levels with respect to each outcome.

Data will be sourced from external organisations as described in the below flow chart:


Within trial
(Up to 24 months)
Index child
Siblings
Dental practice records
Administrative records
Administrative records
England
NHS BSA
NHS Digital
Northern Ireland
BSO
PAS
England
NHS BSA
NHS Digital
Northern Ireland
BSO
PAS
Longitudinal follow up
(up to 10 years)
Index child
Siblings
England
NHS BSA
NHS Digital
Northern Ireland
BSO
PAS
England
NHS BSA
NHS Digital
Northern Ireland
BSO
PAS

14 DATA MANAGEMENT AND TRIAL MONITORING

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

14.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: questionnaires, hospital records, dental records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the study.

Each participating site should maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects

The electronic case report form (eCRF) will be considered the source document for data where no prior record exists and which is recorded directly in the bespoke eCRF.

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's dental record chronologically.

14.2 Data Collection Methods

The study electronic case report form (eCRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded with data being entered in a timely fashion.

Study data will be captured using remote data entry at research sites. Study staff will be trained and delegated the duty of eCRF completion. Training will be given to delegated staff at the Site Initiation Visit.

See section 12: Safety reporting for details on how to report SAEs.

Questionnaires will be completed electronically via a link sent out to parents/primary caregivers. Follow up via telephone or post may occur if questionnaires are not completed electronically.

14.3 Monitoring

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

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This

will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g., enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.7.

14.3.1 Central Monitoring

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the Trial Monitoring Plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be returned to the site in the form of data queries. Data queries are processed entirely through the eCRF system and must be responded to by the site team. Sites will respond to the queries providing an explanation/resolution to the discrepancies directly on to the trial database.

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

14.3.2 Clinical Site Monitoring

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

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

14.4 Risk Assessment

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

- Sponsor representative (s)
- Chief Investigator
- LCTC workstreams

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

The CHOICE trial is determined to be a low risk trial.

14.5 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision

of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

eCRFs will be labelled with a unique trial participant number. Identifiable data will be transferred to the LCTC through the e-consent system when a participant provides consent to the study and enters their contact details. The transfer of identifiable data is disclosed in the PISC.

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

The central research team in the School of Psychology at Queen's University Belfast will be responsible for questionnaire completion at 12 month and 24 month and organising the 24 month dental examination, and therefore will be required to receive contact details including name, address, email and telephone details. Contact details will also be passed on if consent is given to be contacted regarding the qualitative interviews. The contact information will be collected on the e-Consent form on the trial database at trial entry. This data will be transferred electronically and securely to the team at Queen's University Belfast. Queen's University Belfast has appropriate technological and organisational measures in place so as to ensure the appropriate security of personal data, including protection against unauthorised or unlawful processing and against accidental loss, destruction or damage.

Questionnaire data collected in the trial database at LCTC will be transferred electronically and securely to research teams at Queen's University Belfast for analysis.

Audio recordings for the DR-BNI interviews and qualitative interviews will be transferred electronically and securely from the dental practices to the central research team at Queen's University Belfast.

The LCTC, as part of The University of Liverpool, will preserve the confidentiality of participants taking part in the study. Queen's University Belfast is registered as a Data Controller with the Information Commissioners Office.

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

A data sharing agreement will be in place between Queen's University Belfast and NHS Digital, NHS BSA, BSO and PAS to safeguard the confidentiality of personal identifiable data transfer between the two organisations. Data will be transferred using a Secure File Transfer platform.

For the ENCOURAGE sub- study, saliva samples will be collected from dental practices and stored in -20°C freezers. They will be collected by courier and delivered to university freezers for longer term storage at -80°C. All samples will be sent by courier from universities to Queen's University Belfast. Samples will then be sent from Queen's University to Metabolon (USA) for metabolomics analysis. Microbiome and mycobiome analysis will be undertaken at Queen's University Belfast. Pseudonymised data will flow from Metabolon to the ENCOURAGE CI at Queen's University. The ENCOURAGE CI will also have access to the microbiome and mycobiome data. ENCOURAGE data will then be sent to LCTC for integration with CHOICE data.

14.6 Quality Assurance and Control

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

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

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

14.7 Records Retention

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

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File and the applicable participant dental records, for the full length of the trial's retention period, and will arrange for confidential destruction at the end of this period as instructed by the Sponsor / LCTC.

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

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, IMP manufacturers and distributors, third-party vendors providing randomisation and IMP allocation systems, etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Statement of Compliance

The trial will be carried out in accordance with:

- UK policy framework for health and social care research
- The World Medical Association Declaration of Helsinki (1996) and the following updates Edinburgh (2000), Seoul (2008) and Fortaleza (2013)
- The Human Tissue Act (2004)
- Organisation Standard Operating Procedures (the teams working at LCTC and Queen's University Belfast will follow their own Organisation's SOPs)
- Principles of Good Clinical Practice
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and TIDIER

15.2 Ethical Considerations

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

The specific ethical issues relating to participation in this trial are considered to be:

Informed consent in a paediatric population

The appropriate adult providing consent on behalf of the minor participant will have an interview with the Investigator, or a delegated member of the investigating team, during which opportunity will be given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They will be provided with written information and contact details of a member of the research team at the centre, from whom further information about the trial may be obtained, and will be made aware of their right to withdraw the child from the trial at any time without the child or family being subject to any detriment in the child's treatment. Children will receive information, according to their capacity of understanding, about the trial and its risks and benefits.

Where children have their final dental assessment in school, children will be asked by the clinician if they can check their teeth using a mirror and cotton wool to dry the teeth. This is the usual procedure in surveys of child dental health conducted in the UK. On rare occasions, a child does not wish their teeth to be examined and their consent is not given. In this case, their wish is entirely respected and no assessment is made.

15.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and Queen's University Belfast as Sponsor for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.4 Protocol Deviation and Serious Breaches

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

15.4.1 Non-Serious breaches

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

15.4.2 Serious breaches

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

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

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.
The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to the REC.

Breaches confirmed as 'serious' will be reported to REC within 7 days by the LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.
Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.
Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

16 INDEMNITY

Queen's University Belfast holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating dental practice continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the dental practice's duty of care, or any negligence of the part of dental practice employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

17 PUBLICATION AND DISSEMINATION

17.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).
The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.
Any publications arising from this research will be reviewed appropriately prior to publication.

17.1.1 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the CHOICE Consortium which will also be named at the manuscript head.

17.2 Dissemination to Key Stakeholders

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

Outputs and dissemination trial will be reported in peer reviewed scientific articles and scientific conferences.

There will be PPI input for dissemination, capturing PPI impact and for producing a PPI publication at trial end.

17.3 Data Sharing

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

18 CHRONOLOGY OF PROTOCOL AMENDMENTS

18.1 Version 1.0 (22/11/2022)

Original Approved version

18.2 Version 2.0 (Date TBC)

Amendments were required to Version 1.0 of the protocol to add ENCOURAGE as a sub-study and to make changes to how potential participants are contacted about CHOICE. The following changes have been made to the protocol:

- ENCOURAGE sub-study outcomes and objectives were added. (Section 3, page: 14)
- The region Cheshire and Merseyside has been amended to The North West (Section 3, page 14)
- The roles and responsibilities of the ENCOURAGE Research team have been added. (Section 4.7, page: 20)
- Protocol contributors were updated. (Section 4.9, page 21)
- The Exploratory/ Translational objectives were updated to include ENCOURAGE objectives. (Section 6.1.4, page: 24)
- ENCOURAGE outcomes have been added to the outcomes table. (Section 6.2, page: 25)
- A change has been made to allow face-to-face remote delivery of the intervention if a parent is unable to attend the practice. (Section 9.2, page 31)
- A change has been made to extend the window for the intervention visit within 6 weeks to within 12 weeks. (Section 9.2, page 31)
- It has been clarified that Dental Nurse training on the intervention can take place in person or online. (Section 9.2, page 32).
- Updates have been made to Participant Identification and Screening for CHOICE, sites can now contact potential participants before they attend the dental surgery. (Section 10.1, page: 33)
- Updates have been made to Informed consent to state that the PISC for the main trial can be sent/emailed to potential participants before they are seen at the dental surgery. Text has also been added regarding consent being returned by post or email for the implementation study and a statement highlighting the addition of ENCOURAGE consent on the main PISC has been added. (Section 10.1, page: 33)
- The Randomisation process has been updated as randomisation system in now part of the study database. (Section 10.5.1 and 10.5.2, page: 36)
- A change has been made to extend the window for the intervention visit within 6 weeks to within 12 weeks. (Section 10.6, page 37 and 10.8, page 39)
- ENCOURAGE has been added to the Table for Assessment and Follow up. (Section 10.8, page: 38)
- A statement has been added to highlight the website developed by Parenting NI. (Section 10.8.1, page: 39)
- Information has been added to participant withdrawal about ENCOURAGE. (Section 10.9.2, page: 41)
- A change has been made to extend the running of the SWAT to outside of the length of the internal pilot (Section 11, page 43 and 44)
- Details of ENCOURAGE sub-study have been added. (Section 11.2, page: 45)
- Confidentiality section updated to include details regarding the saliva samples collected for ENCOURAGE. (Section 14.5, page: 62)
- Human Tissue Act added. (Section 15.1, page: 65)

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20 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

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