Protocol

A randomised controlled trial to measure the effects and costs of a dental caries prevention regime for young children attending primary care dental services

Acronym: NIC-PIP **Northern Ireland Caries Prevention In Practice Trial**

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
AR	Adverse Reaction
BASCD	British Association for the Study of Community Dentistry
BDA	British Dental Association
BSO	Business Services Organisation
CDO	Chief Dental Officer
CDS	Community Dental Service
CI	Chief Investigator
CONSORT	CONsolidated Standards Of Reporting Trials
CPD	Continuing Professional Development
CRF	Case Report Form
CTA	Clinical Trial Authorisations
CTU	Clinical Trials Unit
EudraCT	European Clinical Trials Database
FGDP	Faculty of General Dental Practice
GCP	Good Clinical Practice
GDP	General Dental Practitioner
GDS	General Dental Service
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICH	International conference of Harmonisation
IDMC	Independent Data Monitoring Committee
IMD	Index of Multiple Deprivation
INVOLVE	A national advisory group, funded by the National Institute for Health Research (NIHR), whose role is to support and promote active public involvement in NHS, public health and social care research
ISRCTN	International Standard Randomised Controlled Trial Number Register
MDM	Multiple Deprivation Measure
MHRA	Medicine and Healthcare Products Regulatory Agency
NIC-PIP	Northern Ireland Caries Prevention in Practice Trial
NIMRA	The Northern Ireland Statistics and Research Agency
PI	Principal Investigator
ppm F	Parts per million Fluoride
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SES	Socio-economic Status
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TPMG	Trial Project Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UIAC	User Involvement Assurance Committee

1 TRIAL SUMMARY

1.1 Trial Phase: Phase IV (pragmatic trial)

1.2 Trial Objective: To compare over a 3 year period the costs and effects of 22,600 ppm fluoride varnish, 1,450 ppm fluoride toothpaste and toothbrush and standardised health education, provided twice a year, as a preventive package, with standardised health education provided twice a year alone.

1.3 Patient Population: Healthy, female and male caries-free children aged 2 and 3 years old at recruitment who are regular attenders at primary care dental services in Northern Ireland.

1.4 Trial Setting: The General Dental Service in Northern Ireland.

1.5 Trial Intervention: Prevention Package

Fluoride varnish applied two times per year for three years

Active Ingredients:	Sodium Fluoride
Study Dosage:	22,600 ppm F
Route of Administration:	Intraoral/Topical – Varnish

Fluoride toothpaste (plus toothbrush) supplied twice per year

Active Ingredients:	Sodium Fluoride
Study Dosage:	1,450 ppm F
Route of Administration:	Topical – dentifrice

Standardised health education delivered by the dentist or hygienist.

1.6 Concurrent Control: Standardised health education delivered by the dentist or hygienist.

1.7 Total Sample Size: An estimated 2356 children attending approximately 40 dental practices will be invited for eligibility assessment for this trial. We aim to recruit 1200 participants in total.

1.8 Method of Participant Assignment: Participants will be individually randomised after the person with parental responsibility has provided informed consent and their eligibility checked.

1.9 Blinding: A placebo will not be used so the allocated interventions will not be blind to parents, children or their dentists. Strenuous efforts will be used to conceal the allocated intervention from the dentists undertaking outcome examinations.

1.10 Examination Points: Baseline and 3 years

1.11 Primary Outcome: The proportion of children converting from caries free to caries active (cavitation into dentine) over three years

1.12 Secondary Outcomes: The number of carious surfaces (caries into dentine) in the primary dentition in children who convert from caries free to caries active states; episodes of pain and extraction of primary teeth; other adverse events; costs

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2 BACKGROUND

2.1 Dental Caries.

Although dental caries is a preventable disease it is a persistent public health problem, with little change in the prevalence in young children over the last 20 years.[1] Caries is closely associated with social deprivation resulting in large geographical and social inequalities across the UK. The last national child dental health survey[1] showed that in 2003 43% and 61% of 5-year-olds in England and Northern Ireland respectively had caries; 10 years earlier, the figures were 45% and 60%. Over the last 10 years the proportion of parents taking children under 3 years to the dentist increased from 42% to 54%[1]; evidently this favourable change in visiting patterns has not been translated into reduced levels of tooth decay in the population.

2.2 Progression of Dental Caries.

Few prospective studies have been undertaken to provide an understanding of how the disease behaves longitudinally.[2] A recently completed prospective cohort study[3] followed 739 children aged 3 to 6 years attending 50 dental practices in the North West of England over a 3 year period. This study demonstrated a stark difference between children who present with and without the disease at their first visit to the dentist. Over the study period 25% of caries free children developed caries, by contrast 72% of those with the disease at initial presentation developed further cavities. No matter what age a child contracted the disease it progressed at the same rapid rate. An important finding of this study was that more cases (children with caries) arose from the initially caries free population (N=155, 21% of the total population and 25% of the population who were caries free at first attendance) than from those who present with the disease at their first visit to the dentist (N=118, 16%). BSO data shows that this situation is mirrored in Northern Ireland; 25% of 2-3-year-old children have the disease at initial presentation but 35% who are caries free at their first visit go on to develop the disease over a 3 year period. Once a child contracts the disease there is a significant impact on their quality of life and that of their family. Children with caries have an 18.8% chance each year of an unscheduled visit due to toothache and an 11% chance of an extraction each year.[4] As adverse outcomes are so common in children with the disease, the priority should be prevention, with a primary focus of maintaining the caries free children in that state. Dentists cannot prevent the disease starting in children who present for the first time already with caries; these children should be considered as a separate population; their dental care needs are quite different and are complicated by the effects of restorative treatment.

2.3 Prevention of Dental Caries

The need to improve preventive care provided by dentists has moved up the policy agenda following the publication of the Primary Dental Care Strategy for Northern Ireland[5] in 2006, which placed a strong emphasis on prevention of caries in general practice, and the subsequent Oral Health Strategy for Northern Ireland in 2007[6], which sets targets for reduction in the caries levels of 5-year-olds. The introduction of new, locally commissioned NHS dental contracts in England and Wales in April 2006 also means that strengthening the evidence base for prevention is important for policy makers and the NHS. One of the main reasons for changing NHS dental contracts was to encourage prevention, however the new contract in England has been heavily criticised by the dental profession and NHS managers[7] and more recently by the House of Commons Health Select Committee[8] for offering little incentive for dentists to provide preventive care. Indeed one of the recommendations of the Health Select Committee report was that *'the Department of Health undertake research to determine the extent to which the provision of preventive advice is*

being given and its cost-effectiveness.' This emphasis on prevention is also seen in the Darzi report[9] and the Primary and Community Care Strategy.[10] Scotland has decided to retain the centrally funded GDS contract based on capitation for children and fee for item for adults. The Department of Health in Northern Ireland intends to change the GDS contract to move to a locally commissioned model and wants to use the outcomes of this trial to inform preventive aspects of the new contract. So, there is pressure on politicians, policy makers and NHS commissioners in the UK to ensure that effective caries prevention is provided in practice. Unfortunately recent research suggests that the preventive care currently provided by GDPs is ineffective and inequitable.[11] Dentists are ill-equipped in terms of their knowledge[12] and how they present information to their patients[13] to provide an effective service.

2.4 Evidence for Interventions to prevent Dental Caries

Preventive care provided by most dentists is based on health education aimed at reducing sugar intake[12,13] which lacks evidence to demonstrate its effectiveness.[14,15] However, there is good evidence that fluoride-based interventions can have a dramatic effect on the disease. For example in a systematic review of water fluoridation[16] the median of mean differences of studies suggested that a 15% absolute difference in the proportions of children caries free can be expected between fluoridated and non-fluoridated populations. It has been estimated that this equates to a difference of around 40% in caries increment.[17] In England water fluoridation is currently being examined as a means of preventing caries but is not technically, economically or politically feasible in every area of the UK, so other delivery vehicles such as professionally applied fluoride varnish or distributed fluoride toothpaste need to be considered. A Cochrane systematic review of fluoride varnish[18] included 9 RCTs and reported a pooled d(e/m)fs prevented fraction estimate of 33% (95% CI, 19% to 48%; $p<0.0001$). A second systematic review[19] of fluoride varnish used different selection criteria and identified only 3 trials examining primary teeth and concluded that the evidence was inconclusive due to the poor quality of the studies. A subsequently published trial of 2-4 year old children[20] examined the effect of 22,600 ppm varnish applied twice a year over 2 years and reported a 57% reduction in caries increment compared to a control group. Another recent trial in the USA[21] investigated the use of 22,600 ppm varnish on infants with a mean age of 1.8 years resident in an area supplied with artificially fluoridated water at 1ppm. Caries incidence was lower in those receiving fluoride varnish twice a year than in a counselling only control (OR 3.77 (95% CI 1.88-7.58) and no adverse events were reported.

A Cochrane review of fluoride toothpaste use[22] in children aged 5-16 years reported clear evidence that fluoride toothpastes are efficacious in preventing caries in permanent teeth but there was little information concerning the primary dentition or adverse effects. Similar findings were also reported by

another systematic review of toothpastes published around the same time.[23] An RCT in the North West[24] testing fluoride toothpaste provided through the post to children from birth to 5-years-old reported a 16% difference in increment and an 8% absolute difference in the proportion of caries free children receiving 1450ppm toothpaste compared to a control group. A Cochrane systematic review examined the effectiveness of any fluoride agent (gel, varnish, mouth rinse) combined with toothpaste[25] and reported a D(M)FS pooled preventive fraction of 10% (95% CI, 2% to 17%; p = 0.01) in favour of a combined regimen over toothpaste alone but the significant difference in favour of the combined use of fluoride varnish and toothpaste accrued from a very small trial and appears likely to be a spurious result. The risks associated with these two interventions are small for the age group under investigation. A follow up study[26] of participants in the NW toothpaste trial[24] compared the prevalence of fluorosis in the study groups and reported a slight increase in prevalence of TF score 3 (an index of fluorosis) but no increase in the overall prevalence of developmental defects of enamel. Recent work shows that fluorosis risk is related to an elevated fluoride intake for all of the first 3 years of life[27] but that the first 2 years of life are the period with greatest risk.[28]

2.5 Rationale for this trial.

Although sub-optimal, the available literature has informed the contents of *Delivering Better Oral Health an Evidence Based Toolkit*[29] national guidance that has been circulated by the Department of Health to every dental practice in England. The fluoride interventions to be investigated in this proposal are identified by the Toolkit and the approach taken in this trial; focusing on caries free children is also supported by the Toolkit, which recommends application of the interventions to all children attending dental practice, the majority of whom will be caries free at their first attendance. This reasoning was informed by the outcomes of the North West cohort study[3] and because there are no effective screening tools to accurately and reliable identify the children who will develop caries.[30] The effectiveness of the intervention to be tested and the impact on NHS costs are unknown and need to be tested in primary care.

If the technologies tested in this trial are effective at preventing caries and reducing costs it will change how dentistry is provided for young children both in the UK and internationally. If the interventions are shown not to be an efficient use of resources this will also influence policy and commissioning, to perhaps focus prevention resources on population interventions such as water fluoridation.

3 TRIAL AIMS and OBJECTIVES

3.1 TRIAL AIM

The aim of this study is to measure the costs and effects of a 'preventive package' in keeping young children who regularly attend primary care service free of dental caries, compared with standard health education alone. The preventive package comprised of:

- Fluoride varnish containing 22,600 ppm fluoride applied twice a year
- A 50 ml tube of fluoride toothpaste containing 1,450 ppm fluoride provided twice a year
- A toothbrush provided twice a year
- Standardised, evidence-based, dental health education provided twice a year.

3.2 TRIAL OBJECTIVES

3.2.1 To compare over a 3 year period the effectiveness of 22,600 ppm fluoride varnish, 1,450 ppm fluoride toothpaste, toothbrush and standardised health education, provided twice a year, as a preventive package, with standardised health education alone provided twice a year in:

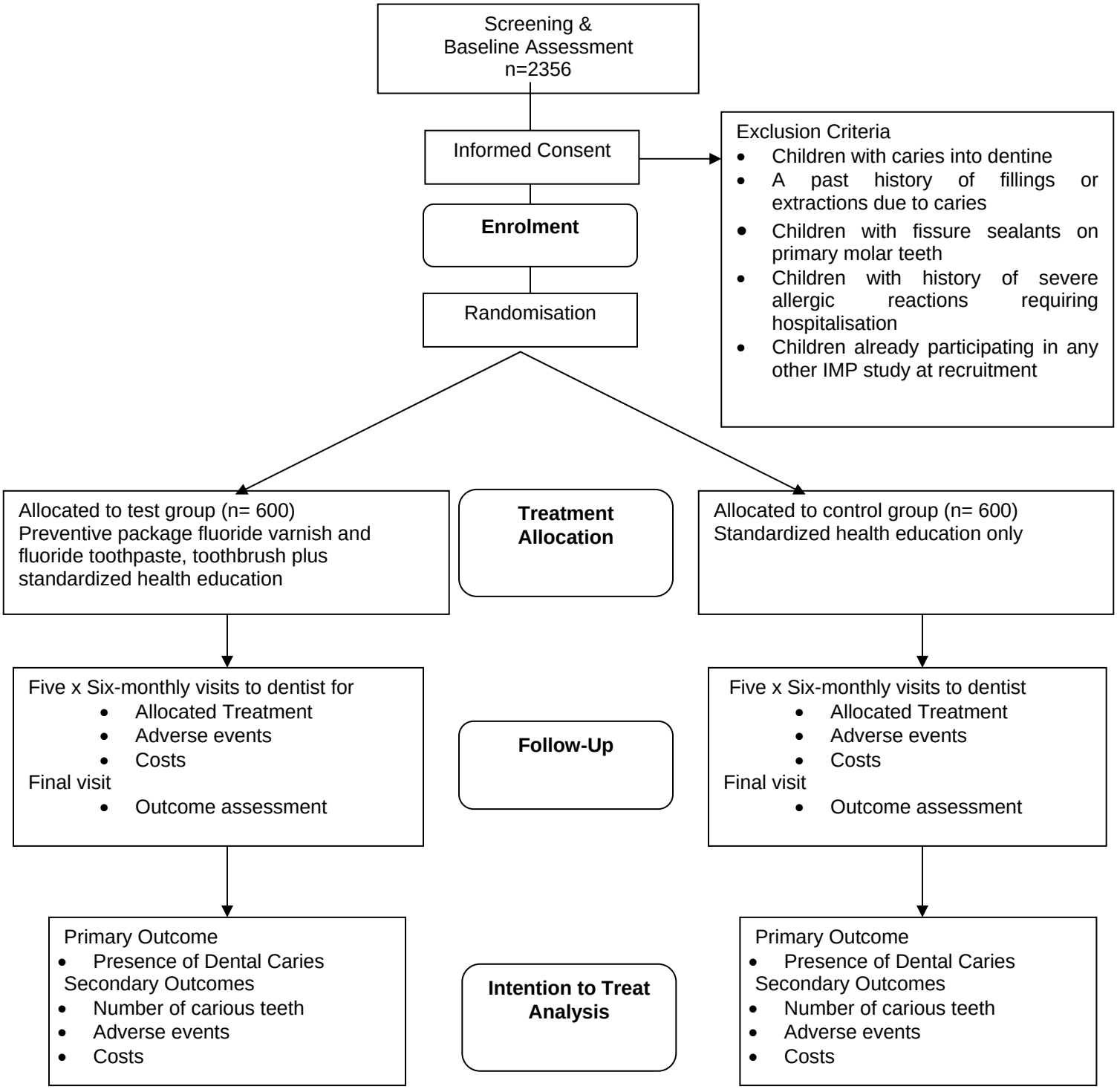
- preventing the conversion of children from caries-free to caries-active states in the primary dentition
- reducing the number of carious surfaces (caries into dentine) in the primary dentition in children who convert from caries free to caries active states
- preventing episodes of pain and extraction of primary teeth in 2 and 3 year-old children who are caries free at baseline and who attend primary care dental services.

3.2.2 To compare over a 3 year period the costs of dental care in a group receiving 22,600 ppm fluoride varnish, 1,450 ppm fluoride toothpaste, toothbrush and standardised health education, provided twice a year as a preventive package with a group receiving standardised health education alone provided twice a year, in 2 and 3 year-old children who are caries free at baseline and who attend primary care dental services.

4 TRIAL DESIGN

Northern Ireland Caries Prevention in Practice Trial (NIC-PIP) is an individually randomised, two-compartment, parallel group phase IV pragmatic trial. Children will be randomised 1:1 into two groups as shown in Figure 1

Figure 1: Trial Schematic



4.1 Trial Participants

Participants will be children aged 2 and 3 years who attend GDS practices in Northern Ireland. Delivering Better Oral Health[29] currently recommends that fluoride varnish application should start when child are 3 years of age. However in light of the study by Weintraub et al.[21] in which the mean age of participants on recruitment was 1.8 years and they were resident in a community supplied by fluoridated water and yet there were no adverse events reported, we believe that we can recruit children from 24 months without significant risks to health.

4.1.1 Trial sites will be selected on the basis of the following criteria:

- willingness to participate in the study
- access to a suitable population of children
- have suitable premises and equipment to host recruitment and baseline assessment activities
- agreement to comply with the protocol and GCP requirements of the trial

4.1.2 Children will be eligible to participate in the study if they fulfil the following criteria:

4.1.2.1 Inclusion criteria:

- Children aged 2 and 3 years
- Attending selected GDS practices
- Person with parental responsibility signs a Consent Form

4.1.2.2 Exclusion criteria:

- Children with caries into dentine
- A past history of fillings or extractions due to caries
- Children with fissure sealants on primary molar teeth
- Children with history of severe allergic reactions requiring hospitalisation
- Children already participating in any other IMP study at recruitment

4.1.2.3 Siblings Rule.

Families usually attend the dentist as a unit; therefore a rule is needed to determine the participation of siblings in the trial. The youngest eligible sibling in a family will be randomised and all other eligible siblings will be excluded from the study and receive their NHS dental care in the usual way.

4.1.3 Sample Size & Duration of the trial

It is planned to recruit 1200 children over 6 months from approximately 40 GDS dental practices. Each child will participate in this clinical trial for 36 months.

4.2 TRIAL INTERVENTIONS

The health technology to be tested is simple and easily applied in primary care. Treatments are applied at two visits to the dental surgery each year at approximately 6 monthly intervals (± 4 weeks).

4.2.1 Treatment Packaging, Supply & Accounting of Study Materials

The fluoride varnish and toothpaste will appear in its normal commercial packaging. The supply and accounting for each material are set out in 4.2.2 and 4.2.3.

4.2.2 22,600 ppm of fluoride varnish will be applied to the dried primary teeth of the children by a participating dentist following the product brochure**,** and a fluoride varnish application protocol which describes the process of application for participating dentists. The United Kingdom "Summary of Product Characteristics" will also be made available to the dentists and hygienists**.** One drop of varnish will be applied to the primary teeth (up to 0.25ml) using a micro-applicator. After application parents will be advised not to brush their children's teeth for 24 hours. The date of each application of fluoride varnish will be recorded for each participant by the Investigator or designee using a Fluoride Varnish, Toothbrush/Toothpaste and Dental Health Education record**.** The Fluoride Varnish, Toothbrush/Toothpaste and Dental Health Education record of each child will identify the batch number of fluoride varnish used for each application. The varnish supplier will distribute the fluoride varnish to a pharmacist within the Belfast Health and Social Care Trust, who will store it in a secure location. The trial manager and trial co-ordinator will distribute the varnish to each site as is required and collect and retain empty or expired tubes of varnish.

4.2.3 a free toothbrush and a free 50 ml tube of 1450 ppm of fluoride toothpaste provided twice a year. Parents of children aged 2 but not 3 years will be advised to use a smear of toothpaste and those over 3 years will be advised to use a pea sized blob of tooth paste when brushing their teeth. Photographs of a smear and a pea size blob will be included in the standardised dental health education guide**.** It will be stressed to parents that children must be supervised by an adult when they brush their teeth. **The toothpaste** supplier will distribute the toothpaste and toothbrushes to a pharmacist within the Belfast Health and Social Care Trust. The toothpaste and toothbrushes will be delivered to sites by the trial manager and trial co-ordinator, who will be responsible for ensuring an adequate supply is available. The Investigator or designees will distribute the toothpaste and the toothbrushes to the parent's of participants at each visit. The Investigator or designees will keep a record of the distribution of toothpaste and toothbrushes to each child using a Fluoride Varnish, Toothbrush/Toothpaste and Dental Health Education record. In the event of children not attending for their check up appointments the Investigator or designees will send out reminder letters**.**

4.2.4 Standardised dental health education at each 6 month check up visit by dentists or hygienists following a guide. This will be captured on the Fluoride Varnish, Toothbrush/Toothpaste and Dental Health Education record.

4.2.5 The control group

Children allocated to the control group will attend at 6 monthly intervals and receive the same standardised dental health education at each 6 month visit as the test group using the same guide. The control group will not receive any professionally applied or provided fluoride interventions.

4.2.6 Additional Treatment.

All children who convert from caries free to caries will receive dental treatment, e.g. fillings, extractions in the usual way as prescribed by their dentist. All children who convert from caries free to caries active will continue to receive the trial interventions (both test and control) for the duration of the trial.

4.3 OUTCOME MEASURES

Baseline and outcome examinations will be performed by trained examiners, blinded to the treatment allocation and using the same diagnostic protocol.

4.3.1 Primary Outcome measures

The primary outcome is to measure the proportion of children that convert from caries free to caries active (caries into dentine) children.

4.3.2 Secondary Outcome measures

- The number of carious surfaces (caries into dentine) in the primary dentition in children who convert from caries free to caries active states.
- The number of episodes of pain and number of extractions of primary teeth in 2 and 3 year-old children who are caries free at baseline and who attend primary care dental services.
- The costs of dental care over a 3 year period.

4.4 DATA ANALYSIS

As the trial is pragmatic in nature, analyses will follow an intention to treat approach whereby the data from all participants will be analysed according to the group to which the child was allocated.

5 TRIAL PROCEDURES

5.1 RECRUITMENT OF TRIAL SITES

The BSO has identified 77 practices in Northern Ireland that have more than 50 registered children aged 2-4 years. We will focus our efforts on recruiting from these practices in the first instance to reduce the number of practices required and to reduce costs. The trial will be well publicised amongst the dental community in Northern Ireland by communications from the Chief Dental Officer (CDO), the Health Boards and the British Dental Association (BDA). Practices will be formally invited to participate in the trial by a joint letter from the Principal and Chief investigators. Recruitment will be aided informally by members of the team, who have a strong influence among practitioners, speaking directly to practices. Once interested practices have been identified members of the team will visit the practices to explain the study in a face to face meeting.

Sites that show an interest in the trial will be visited by the trial team who will complete a site assessment form. Sites that are eligible for inclusion in the study will be invited to sign a formal contract with the University of Manchester and Belfast Health and Social Care Trust. The practice principal who signs the contract will be the Local Investigator at each GDS site.

5.2 SCREENING & SELECTION OF CHILDREN

Practices (or the BSO for non-computerised practices) will identify children in the correct age group who are registered with each practice and provide a list of potential participants for each GDS site.

5.3 SCREENING CLINICS

Once potential children have been identified, the Investigator or designees will block-book dedicated trial sessions at the practices. A separate randomisation schedule will be prepared by the Clinical Trials Unit (CTU)

for each recruiting centre using randomised permutated blocks. The block lengths will vary to ensure the centres are blind to patient allocation.

- The Investigator or designee will send out an invitation letter and trial information leaflet to parents of identified children asking if they would like to participate in the trial.
- The invitation letter will be sent out at least one week prior to the appointment and parents will be encouraged to ring their practice to make an appointment or if they require further information. The invitation letter will stress that the adult with parental responsibility for the child must accompany the child when they attend for assessment.

Each investigator will retain a list of all patients screened as well as enrolled in the trial through an Eligibility Assessment Form. The screening log will be retained in the investigator's site file and a copy submitted to the CTU.

5.4 INFORMED CONSENT PROCEDURE

When each person with parental responsibility and child arrives at a screening session the study will be explained to them by the trained Investigator or designee. The external CDS and/or independent dentists (who will undertake the baseline examinations) will consent the children into the trial. Parents of eligible patients will be informed of the aims of the study, the mechanism of treatment allocation, the procedures, possible adverse events and hazards to which the children may be exposed to. They will be informed as to the strict confidentiality of the patient data, but that the dental records may be reviewed for trial purposes by authorised individuals other than their treating dentist. It will be emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants and this will not prejudice the patient's subsequent care.

Informed consent forms will be completed for each participant by an adult with parental responsibility. Documented informed consent must be obtained for all patients included in the study before they are registered and randomised in the trial. This must be done in accordance with the national and local regulatory requirements. The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that *"the written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative"*. Original consent forms will be stored with each participant's clinical notes at each site, with one copy given to the person with parental responsibility and another stored in the investigator site file.

5.5 REGISTRATION / RANDOMISATION PROCEDURE

Children who meet the eligibility criteria and whose person with parental responsibility have given written informed consent will be enrolled on the clinical trial.

The investigator (or designee) will contact the Clinical Trials Unit (CTU) on a dedicated trial telephone line and the children will be centrally randomised to one of the two treatment groups. The children will initially be identified at registration by their initials, date of birth and gender only. Once all of the eligibility criteria have been verified by the CTU they will provide the investigator with confirmation of the treatment allocation and the unique Participant ID assigned. Written confirmation of the child entering into the trial will be sent to the investigator. Participant IDs will be assigned sequentially as children enter the trial. The Participant ID will be used for the purpose of participant identification and data collection during the study.

Registration forms which will document the child's eligibility should also be faxed to the CTU.

Registration
Telephone: 028 9063 3594 (Mon- Fri, 09:00-17:00)
Fax: 028 9063 3554

5.6 RETENTION OF CHILDREN IN THE TRIAL

All children will be sent 6 monthly appointments for a check up, along with a questionnaire for the person with parental responsibility through the post by the Investigator or designee at GDS practices. The Investigator or designee will also telephone or text parents of participants the day before recall appointments to remind them to attend. Parents of children who fail to attend their appointments will be sent a follow up letter and another appointment will be made.

5.7 WITHDRAWAL PROCEDURE

Person with parental responsibility and children, where appropriate, have the right to withdraw from the trial at any time for any reason. Dentists also have the right to withdraw a child from the trial at any time. Should a person with parental responsibility decide to stop, an off study form should be filled in and sent to the CTU within one week of the event.

The withdrawal will be noted on the Off Study Form within the CRF.

5.8 MONITORING OF RECRUITMENT

During the six month recruitment phase the CTU will collate information on recruitment at each site and provide yearly reports on recruitment rates to the

IDMC. The trial manager will be responsible for checking the number of participants recruited at each screening session and checking these lists with the CTU. The CTU will provide reports to the Trial Steering Committee (TSC). 6 Monthly progress reports will be sent by the CI to the HTA.

5.9 TRIAL ASSESSMENTS

The principal outcome measures will be assessed by baseline and outcome examinations, secondary outcome measures will be assessed by a questionnaire for person with parental responsibility and the site clinical record form which will be completed by the Investigator or designees. The assessment programme for the trial is set out in Table 5.9.

Table 5.9	Screening Baseline	6 mth	12 mth	18 mth	24 mth	30 mth	36 mth
Informed Consent	x						
Inclusion/Exclusion Criteria	x						
Demographic Data	x						
Randomisation/ Registration	x						
Baseline caries assessment	x						
Parent/guardian questionnaire*		x	x	x	x	x	x
Clinical data (on symptoms and treatment received) collected by Investigator or designees*		x	x	x	x	x	x
Assessment of adverse events*		x	x	x	x	x	x
Outcome caries assessment							x

* these data also to be collected at unscheduled visits

5.9.1 Clinical Outcomes measured by Examination

The primary outcome measure is the conversion of caries free children to caries active (caries into dentine) children. Secondary outcome measures include the number of carious surfaces (caries into dentine in primary teeth) that develop in children who convert from caries free to caries active. Baseline and outcome examinations will be performed by a trained examination team consisting of a CDS and/or independent dentist examiner and CDS and/or independent dental nurse using a standardised diagnostic protocol.

5.9.1.1 Calibration of Examiners

Before both baseline and outcome examinations, training exercises will be held on at least 25, 4-6 year old children in a primary school. All examiners will examine each child twice and inter and intra-examiner agreements for recording carious teeth will be assessed using the Kappa statistic. Within and between examiner agreements for recording caries status at tooth level must exceed a kappa score of 0.70 or further training will be provided and the calibration exercise repeated until acceptable levels of agreement are achieved. The results of baseline and outcome calibration will be made available to the co- sponsors, the Trial Steering Committee and the Independent Data Monitoring Committee.

5.9.1.2 Ongoing tests for Inter and Intra-examiner reliability

Half-way through the outcome examination period a second calibration exercise will be undertaken on at least 25, 4-6 year old children in a primary school. All examiners will examine each child twice and inter and intra-examiner agreements for recording carious teeth will be assessed using the Kappa statistic. Inter and intra-examiner agreement for recording caries at tooth level must exceed a weighted kappa score of 0.70 or further training will be provided and examination retested until acceptable levels of reliability are achieved. Statistical analysis of outcomes of intra-examiner reliability tests will be available to the co- sponsors, the Trial Steering Committee and the Independent Data Monitoring Committee.

5.9.1.3 Baseline Examination

All baseline examinations will take place within the surgery of the clinical services. Prior to randomisation children will be assessed by the CDS and/or independent dentists to determine if they meet the study inclusion criteria using an eligibility assessment proforma. The examiners and dental nurses will also ensure that the recruitment and randomisation procedures are followed according to the protocol. The CDS and/or independent examining dentists, after appropriate training will be responsible for taking informed consent. Assessment will be undertaken by visual examination. Baseline and outcome data will be recorded onto a caries data collection form.

5.9.1.4 Outcome Examination

Outcome clinical examinations will be conducted at 36 months (± 2 months) using the same examination criteria employed at baseline. The consent procedure of each participant will request permission from parents to take this approach at outcome measurement. After the outcome examination, the examining dentist will complete a form stating whether each participant has or has not completed the study according to protocol specifications. The Caries Data Recording Form will be completed and stored at each site and copies forwarded to the CTU at the end of the outcome examination period.

5.9.2 Outcomes measured from site records and questionnaire for person with parental responsibility.

A number of secondary outcome measures will be collected by Investigator or designees and parentally completed questionnaires.

5.9.3 Clinical data collected by Investigator or designees

The Investigator or designees will collect information on symptoms reported and treatment received by each child at each visit (both planned 6 monthly check-ups and unplanned symptomatic visits) using a site clinical record form.

5.9.4 Data Collected from questionnaire for person with parental responsibility

A piloted questionnaire for person with parental responsibility will be used to identify any unscheduled visit to other dentist services and other episodes of toothache not severe enough to require a visit to the dentist. The questionnaire will collect data on:

- Number of episodes of pain requiring an unscheduled visit to a dentist other than the practice the participant is registered with
- Number of episodes of toothache (not requiring a visit to a dentist) and its severity
- Number and type of treatment provided by services other than the child's primary care dental services

Parents will be sent the questionnaire by the Investigator or designee at the same time as the 6 monthly appointments for check-ups. The Investigator or designees will collect the completed questionnaires at the check-up visits and sent to the trial manager which will be stored in the trial master file.. A second questionnaire with a reminder letter will be sent by the Investigator or designee to non-responders one month after the initial letter was sent to parents.

5.10 DATA COLLECTION & RECORDING

All data required according to this protocol will be recorded on the case report form (CRF). All trial data will be recorded directly into the CRF and questionnaires rather than source notes, however Dentists will be expected to keep up-to-date clinical records. All entries on the CRF, including corrections will be made by designated staff. The CRF's will be collected as per the CRF submission schedule and forwarded to the CTU:

Clinical Trials Unit
(Data Management Office)
Education and Research Centre
The Royal Hospitals
Grosvenor Road
Belfast
BT12 6BA

5.11 DATA MANAGEMENT

All data will be submitted to the CTU according to the data submission schedule. All data will be anonymised and reviewed for completeness. The data will be entered into the clinical trial database and verified through the use of programmed edit checks for accuracy and completeness. Any errors or omissions in the data will be raised for resolution by the practices in the form of data clarification forms. The signed original and resolved data clarification forms will be returned to the CTU so the resolutions can be entered into the database. The corrected data and a complete audit trail of corrections will be retained. All data management personnel will be trained and follow standard operating procedures (SOPs) to ensure a consistent approach to all data management activities.

6 PHARMACOVIGILANCE

6.1 DEFINITION OF ADVERSE EVENTS (AE)

The EU Clinical Trials Directive 2001/20 provides the definitions given in table 6.1

Table 6.1: Terms and definitions for AEs

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Unexpected Adverse Reaction (UAR)	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in: The Summary of Product Characteristics (SPC) for that product (for products with a marketing authorisation) or The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)
SAE (SAE) **Serious Adverse Reaction (SAR)** **Suspected Unexpected Serious Adverse Reaction (SUSAR)**	Respectively, any AE, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation* • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect • is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre- existing condition, including elective procedures that have not worsened, do not constitute an SAE.

6.2 ELICITING ADVERSE EVENT INFORMATION

The investigator is to record all directly observed AEs and all AEs spontaneously reported by the parent/guardian. In addition, the parent/guardian of each trial participant will be questioned by their dentist about AEs at each clinic visit following initiation of treatment. A typical question that will be asked will be: *Since your last clinic visit, has your child had any health problems?*

6.3 ASSESSMENT OF INTENSITY

The local investigator at each site will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE.

For purposes of consistency, these intensity grades are defined as follows:

- **MILD** Does not interfere with participant's usual function
- **MODERATE** Interferes to some extent with participant's usual function
- **SEVERE** Interferes significantly with participant's usual function

Note the distinction between the gravity and the intensity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity but would not be classified as serious unless it met one of the criteria for serious events listed above.

6.4 ASSESSMENT OF CAUSALITY

Each AE should be clinically assessed for causality based on information available and reviewed as new information becomes available. i.e. relationship of AE to the trial medicament. For the purpose of this trial the relationships will be defined as follows: Definitely, Probably, Possibly, Unlikely, Not Related.

6.5 RECORDING ADVERSE EVENTS IN THE CASE REPORT FORMS

Information on AE's must be evaluated by each participant's dentist (Local Investigator) and recorded on AE event forms. The local investigator will also be asked to assess the possible relationship between the AE and the investigational medication. Once causality has been determined, only AR's, SAE's and SUSAR's defined in the table in section 6.8 will be recorded on the Case Report Form.

6.5.1 Pre-existing Conditions

In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical examination form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

6.5.2 Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of a serious AE. If a patient undergoes a surgical procedure that was planned prior to entry into the trial, and the surgery is not performed due to a worsening of a baseline condition, this should not be reported as an AE.

6.6 FOLLOW UP OF ADVERSE EVENTS

All recorded AEs that meet the criteria as outlined in table 6.8 will be followed until they are resolved or the investigator assesses them as chronic or stable or the participant's participation in the trial ends (i.e., until a final report is completed for that participant). In addition, all serious AEs and those non-serious events assessed by the investigator as possibly related to the investigational medication/product should continue to be followed even after the participant's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as chronic or stable.

Resolution of such events is to be documented on the appropriate case report form.

6.7 ADVERSE EVENT REPORTING PERIOD

The AE reporting period for this trial begins upon enrolment in to the study and ends at the 36 month visit. All AEs identified in Table 6.8 that occur in trial participants during the AE reporting period specified in the protocol **must** be reported to the CTU. In addition, any known untoward event that occurs subsequent to the AE reporting period that the investigator assesses as possibly related to the investigational medication/product should also be reported as an AE.

6.8 REPORTING REQUIREMENTS

6.8.1 Adverse Event (AE) Reporting

This is a Phase IV trial and fluoride varnish has been used routinely in general dental practice for many years. In addition the study by Weintraub et al.[21] investigated the use of 22,600 ppm varnish on infants with a mean age of 1.8 years resident in an area supplied with artificially fluoridated water at 1ppm. and no AEs were reported, therefore the risks to participants is low. This trial will report AEs according to the negligible risk to patients. Therefore only the following events will be reported:

Table 6.8 Reporting criteria for AEs

Adverse events to be reported	Criteria for reporting
Adverse Reaction (AR)	Where the local investigator decides that the adverse reaction is certainly, probably or possibly related to the fluoride varnish
Unexpected Adverse Reaction (UAR)	
SAE (SAE)	• **results in death** • **is life-threatening** • **requires hospitalisation**
Serious Adverse Reaction (SAR)	
Suspected Unexpected Serious Adverse Reaction (SUSAR)	

All AEs set out in the above table will be recorded on the appropriate case report form by each local investigator or designee. The CTU will receive all AE reports from the investigational site on case report forms. The CTU will report all AEs received to the IDMC every 6 months. The CI or designee will provide annual safety reports on the anniversary of approval date to the Ethics committee, regulatory agency and sponsor. The sponsor will accept, as their report, a copy of the Research Ethics Committee annual report.

6.8.2 SAE, SAR and SUSAR Reporting

SAR's, SAEs and SUSAR's will be recorded on an SAE form. Each AE is to be classified by the local investigator at each site as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed. If a SAE occurs, reporting will follow local and international regulations, as appropriate.

In the rare event that the local investigator does not become aware of the occurrence of a SAE immediately (e.g., the trial participant initially received treatment elsewhere), the local investigator is to report the event within 24 hours after learning of it and document his/her first awareness of the AE.

6.8.3 Investigator Responsibilities

All SAEs must be reported by the local investigator at each site to the CTU on a SAE form within 24 hours (or the next working day) of the investigator being aware of the event.

6.8.4 Investigator Procedures

The SAE form should be completed by the responsible local investigator (dentist named on the signature list and delegation of responsibilities log who is responsible for the patient's care). The local investigator will judge the relationship of the intervention\treatment to the event: Definitely, Probably, Possibly, Unlikely, Not Related and to record their judgement on the adverse

events form. In the absence of the responsible investigator the member of the trial team that records the SAE should contact the CTU who will liaise with the CI/PI for the study to determine causality, or a local designee who will make judgements and complete the SAE form as soon as possible. The initial report shall be followed by detailed, written reports within 48 hours for all SAE's, SAR's and SUSAR's.

6.8.5 CI, PI and Trial Manager's Responsibilities

The Trial manager is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the competent authorities (regulatory authorities and central research ethics committees) as follows:

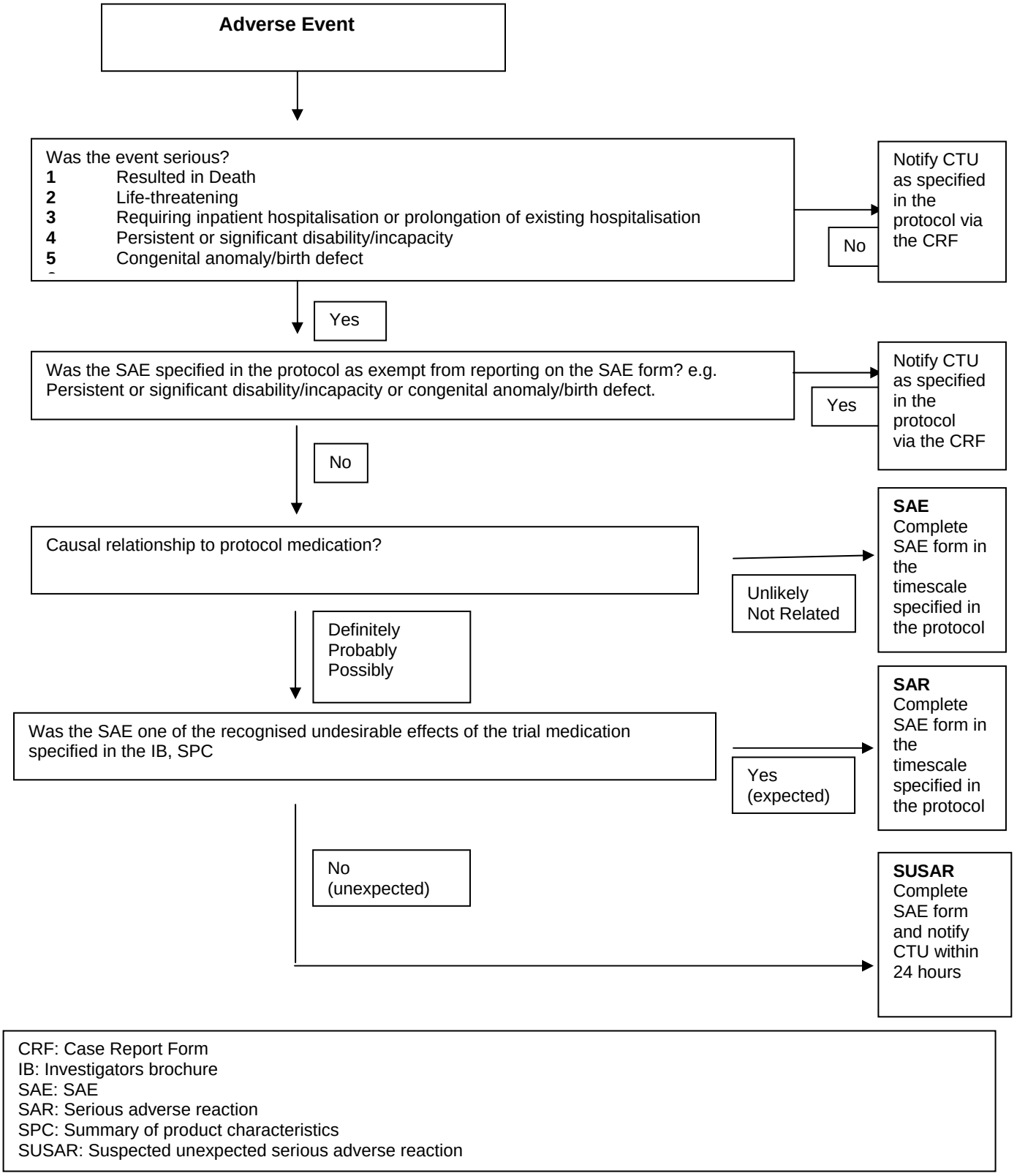
- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.
- The Chief Investigator (or PI) will evaluate all SAEs received for seriousness, causality and expectedness.
- Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities.
- The causality assessment given by the Investigator cannot be overruled and in the case of disagreement, both opinions will be provided with the report.
- Reports of SUSARs will also be sent to other investigation sites
- Copies of expedited reports will be sent to the CI and co- sponsors
- All SAE reports will be sent to the CTU for inclusion in reports

6.8.6 CI, PI and Trial Managers Procedure

- The CTU will receive notification of SAEs from the investigational sites within 24 hours of investigator awareness.
- On receipt of the reported SAE the trial manager will forward the SAE report by fax to Prof Martin Tickle as CI and where due to holiday or absence and the CI is not available this will be sent to the PI, Dr Michael Donaldson for evaluation for seriousness, causality and expectedness.
- The fax notification will be followed up by a phone call to ensure receipt and confirm a timeline for response within 24 hours or a nominated deputy in the event of holidays or sickness
- Prof Martin Tickle and/or Dr Michael Donaldson will evaluate the SAE for seriousness, expectedness and causality
- The trial manager will be notified by email of the outcome of evaluation and expected reporting format, i.e. expedited or annual safety report

- SAEs evaluated as not requiring expedited reporting will be included in the annual report
- SAEs evaluated as SUSARs will be reported to the Sponsors and then the competent authorities immediately after evaluation.
- SUSAR reports may be sent by fax, by email or as electronic documents on a disk.
- Detailed information and reporting forms can be accessed on http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm

Figure 2. Flow Chart of assessing and notification of Adverse Events



CRF: Case Report Form
IB: Investigators brochure
SAE: SAE
SAR: Serious adverse reaction
SPC: Summary of product characteristics
SUSAR: Suspected unexpected serious adverse reaction

7 STATISTICAL CONSIDERATIONS

7.1 SAMPLE SIZE

The principal outcome measure is dichotomous; conversion from a caries free state to caries active in the primary dentition. The sample size is therefore based on measuring an absolute difference in the proportion of children who are free of the disease. The intervention to be tested is 1450ppm toothpaste and toothbrush, standardised health education and 22,600ppm fluoride varnish provided 2x a year over 3 years. We expect to see an absolute difference in the proportion of children with caries after 3 years of 0.1 between test and control groups. This expectation is based on the findings of a trial of 1,450 ppm toothpaste, on pre-school children in the North West[25] which reported 0.08 absolute difference in the proportion of children with caries between test and control groups. In this proposal, as fluoride toothpaste is supplemented with biannual applications of fluoride varnish, we expect to see enhanced efficacy and therefore a 0.1 absolute difference in proportions.

The best data on the event rate for this practice-based population comes from the BSO database rather than epidemiological studies on other populations. Current BSO data shows that 75% of 2 and 3 years olds in Northern Ireland who are registered with a dentist are caries free at first attendance. Over a 3 year period this reduces to only 40% of 5-7 year-old children. A further 35% of children therefore develop caries. If caries free children are selected for the study it is estimated that 47% will develop caries over the three years. A two group chi-square test with a 0.050 two-sided significance level will have 90% power to detect the difference between a proportion of 0.470 and a proportion of 0.370 (odds ratio of 0.662) when the sample size in each group is 510. We assume that 2% will be excluded because of a history of severe allergic reaction and a further 1% for other reasons. We also assume that 75% of children approached will be caries free and a 70% consent rate with an estimated 15% drop-out rate over the 3 years. Therefore we will need to initially invite at least 2356 children to take part in the study, recruiting 1200 children to ensure we have sufficient power at the end of the trial. The recruitment process is summarised in a CONSORT flow chart in **Appendix II**.

We expect the participation of 50 practices in the trial to enable us to recruit sufficient participants. Based on BSO data, these practices (with >50 children in the age band of interest) have on average 71 children aged 2-4 years old providing potentially 3550 children for recruitment. However, if we assume only 80% (2840) attend for assessment and only 75% will be eligible as they will be caries free, leaving 2130, and we expect only 70% of eligible children to provide consent leaving potentially 1491 children who could be recruited into the study. Therefore with a target of 1200 children for recruitment into the trial, this number of practices, plus recruiting from the unregistered population, provides sufficient leeway to take into account eventualities such as recruiting practices with smaller numbers of children, higher numbers of children with caries and lower consent rates than anticipated.

7.2 INTERIM ANALYSIS

The IDMC will be presented with unblinded, interim analyses of AEs in addition to data on recruitment rates. The IDMC will use these data to decide whether to stop the study.

7.3 FINAL ANALYSIS.

All analyses will follow an analysis plan**.** All analyses will be conducted according to the plan which will be agreed in advance by the co- sponsors and the Trial Steering Committee.

All outcome measures stated in the protocol will be fully analysed using generalized linear models adjusting for covariates felt to be of prognostic importance including age and socio-economic status (SES). SES will be measured using the Northern Ireland Measure of Multiple Deprivation (MDM 2005) (The Northern Ireland Statistics and Research Agency NISRA) **(**web-site http://www.nisra.gov.uk/**)**, collected by reference to each participant's home postcode at the baseline of the study. This process will involve matching each participant's postcode to the super-output area using a suitable lookup table. Once a super-output area code is assigned to each record, the MDM 2005 code for each super–output area will be added to each record by reference to the relevant super-output area to MDM code. The index of deprivation MDM (1=most deprived, 860=least) will be categorised into quintiles.

Statistical significance will be at the 0.05 level for all analysis and 95% confidence intervals will be calculated. A binary logistic regression model will be fitted to the primary outcome, whether the child remained caries free or not, with study group, age and socioeconomic status as covariates. Age at randomisation will be included as a continuous covariate and quintiles of SES measured by the MDM as a covariate. A 95% confidence interval for the absolute difference in proportions between the groups will be reported. We will report the unadjusted and adjusted (for age and MDM) odds ratios from the logistic regression model and will specify that the adjusted is the primary analytical approach. We will also undertake a subgroup analysis for deprived/not deprived children by selecting children whose parents are exempt from dental charges or not. This will be formally investigated by means of an "interaction test" of the null hypothesis that the relative efficacy of the two interventions is the same in deprived and non-deprived children. It should be noted, however, that the trial is not formally powered to detect social interaction effects; consequently we would only expect to observe an interaction as being statistically significant, if this were very large.

A secondary analysis will be undertaken with the same covariates using the Huber-White approach within Stata (vce(cluster) to deal with potential dentist clustering effects (also known as sandwich estimator and robust estimator of variance). This technique relaxes the assumption of independence of the observations and can produce the 'correct 'standard errors even if the observations are correlated.

8 HEALTH ECONOMIC EVALUATION

Health economic analysis will compare the total cost to the NHS for dental care in each of the two arms of the trial in accordance with the relative levels of effectiveness for each of the two arms.

8.1 COST DATA

8.1.1 Measurement of direct costs

The market costs of varnish, toothpaste and toothbrushes will be determined by reference to the providing manufacturer. The Investigator or designees will record delivery time and the treatment provided at each visit on the site clinical record form. Delivery time will relate specifically to time spent with the dentist (chair time) and will be recorded to the nearest whole minute. Delivery time will be monetised by reference to implicit average NHS dental pay rates provided by the BSO.

8.1.2 Measurement of indirect costs

Indirect health service costs will be measured from data collected via a questionnaire given to the person with parental responsibility. This questionnaire will identify any non-intervention dental or other health service activity that the child receives whether at participating or non-participating sites. Where treatment other than that directly related to the intervention is received from trial dentists, activity reported by parents will be validated using dentist records. Indirect dental activity time will be monetised as above and other health service activity using PSSRU unit costs. Non-trial dentist treatment time will be imputed based on the average time observed among trial dentists by procedure and monetised as above. Consumables – such as fillings, or fissure sealants will be monetised by reference to commercial suppliers

8.1.3 Measurement of non-health service costs

Direct and indirect non-health service costs will be determined by a questionnaire given to the person with parental responsibility. This will ascertain reported total time taken to accompany the child for a dental visit, and time off work, plus distance travelled. Travel costs will be monetised using AA reference costs per mile. Time costs will be monetised using average earnings in Northern Ireland. Where more than one child is accompanied to the dentist on a particular visit this will be recorded in the questionnaire and time costs apportioned proportionately.

8.2 COST ANALYSIS

We will calculate the present value of cumulative total cost and benefit in the intervention and control groups.

A multiple linear regression model will be fitted to the individual discounted costs per child with group, age and socio-economic status (SES) as covariates. If the assumptions underlying the model are not upheld, robust estimates of the standard errors will be calculated for the estimated parameters. This will generate an assessment of the additional level of investment required to achieve the

measured benefit. Separate calculations will be made of between-treatment differences in cost to parents to identify any between-programme trade-offs. All calculations will be subjected to sensitivity analysis and discount rates of 3.5% for both cost and benefits will be applied.

The incremental cost effectiveness ratio (ICER) will be estimated by dividing the difference in mean discounted costs between the two groups by the difference in discounted proportions that remain caries free. Univariate sensitivity analysis will be performed to determine how robust the calculations for cost-effectiveness are and how sensitive they are to changes in, for example, the implicit cost of staff time. To examine uncertainty in the value of the ICER due to sampling variation, plus uncertainty in the threshold level of cost effectiveness that interventions need to exceed to be considered cost-effective, cost-effectiveness acceptability curves will also be constructed.

The relationship between cost and secondary outcomes such as the number of carious surfaces will be examined in an analogous fashion to that detailed above. The net present value of costs will be divided by the net present value of the number of carious surfaces to ascertain the average cost for carious surface avoided.

9 REGULATIONS, ETHICS and GOVERNANCE

9.1 SPONSORSHIP

The Belfast Health & Social Care Trust and the University of Manchester will be co- sponsors of the study.

9.2 REGULATORY & ETHICAL APPROVALS

The trial will not begin until all the relevant approvals and permissions have been obtained. The trial protocol, informed consent documents and trial related questionnaires will be formally approved by a national ethics body, regulatory agency and the sponsoring HSC Trust research office. In addition the study will seek formal approval from the University of Manchester's ethics committee, to ensure that indemnity is secured for non-negligent harm. Each centre and investigator will also obtain individual approval from a local research ethics committee prior to enrolling children.

The trial will be registered on ISRCTN and CTA and a EudraCT number will be obtained from the MHRA. The University of Manchester and the Belfast Health & Social Care Trust, as co-sponsors of the study, will have responsibility for ensuring that it is delivered to the standards laid down by MHRA.

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong and Edinburgh) (**see Appendix III**), the ICH Harmonized Tripartite Guideline for Good Clinical Practice and the EU directive 2001/20/EC.

The Chief Investigator will take overall responsibility for the conduct of the trial. The investigator at each of the site will sign an Investigator's Agreement agreeing to the Terms and Conditions of participation in the trial which must be in place before the study starts in that centre.

9.3 ETHICAL ISSUES

The risks for trial participants in the intervention groups include allergic responses to the varnish. The varnish contains colophony, which in highly exceptional circumstances, has resulted in allergic reactions and for this reason we will exclude all children who have been hospitalised due to allergic conditions. There might be concerns about the risk of children in the test group developing fluorosis. This is unlikely (see research cited in references in **Appendix IV**) as the varnish will be professionally applied and frequent, standardised advice on the safe use of the toothpaste will be given to all participants. Robust systems for reporting AEs have been described in the protocol. The IDMC can recommend that the trial stops early if there are concerns about the number of AEs or if recruitment is low.

The procedure to be followed by the Chief Investigator if the co- sponsors terminate the study is as follows:

- Notify the Participants and complete the data collection forms as appropriate.
- Notify the relevant Ethical Committee, MHRA and IDMC.
- Ensure all documentation is archived according to the protocol.

9.4 PROTOCOL COMPLIANCE

Each investigator will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee (EC) and the appropriate regulatory authority. Changes to the protocol will require written EC approval/favourable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The investigator will submit all protocol modifications to the regulatory authority in accordance with the governing regulations. Any deviations from the protocol must be fully documented in the case report form and source documentation.

9.5 PATIENT CONFIDENTIALITY

In order to maintain confidentiality, all case report forms, study reports and communications regarding the study will identify patients by assigned patient numbers. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participating GDS practices with a computerised patient database will be asked to search their patient databases to identify children who meet the participant selection criteria and contact the parents of potentially eligible children on behalf of the research team. Members of the research team will be able to request names and addresses of 2 and 3 year old children within eligible practices from

the BSO. This data can be securely provided to GDS without computerised systems.

9.6 GOOD CLINICAL PRACTICE

The trial will be conducted in accordance with the International Conference of Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirements. The Investigators will be thoroughly familiar with the appropriate use of trial medicament and treatments as described in the protocol. The CTU will provide training in and ensure adherence to GCP for all people involved the delivery of the trial

9.6.1 Trial Master File

A Trial Master File will be set up at the beginning of the trial, and held in a secure location by the CTU, within the Belfast Health and Social Care Trust. The essential documents that make up the file will be listed in a SOP and the purpose of each document will be clearly described. The trial will not begin until all the relevant approvals and permissions have been obtained.

9.6.2 Archiving

The study data will be securely archived at The University of Manchester, free of charge to the trial. We will follow the University Code of Good Research Conduct **(**See website http://www/researchsupport.manchester.ac.uk/Governance/ResearchActivity.aspx**)** which requires trial documents to be held for five years after the last publication from the study or for ten years, whichever is longer. The University has an effective document retrieval system in place for archived documents.

9.7 TRIAL MONITORING

9.7.1 Direct Access to Data

The agreement with each investigator will include permission for trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. Consent from a person **with parental responsibility** for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.7.2 Monitoring arrangements

The CI will complete a trial risk assessment outlining any potential hazards of the trial and proposal on how to minimise them. The extent of monitoring for the trial is based on the risk assessment from the CI and directed by the co- sponsors. Monitoring will be an ongoing activity from the time of initiation until closeout and will comply with the EU directive 2001/20/EC and ICH and GCP regulations. All monitoring activities will be documented. Site monitoring visits will be carried out according to the monitoring plan and available SOPs.

9.8 INVESTIGATOR'S REPORTING

The investigator will issue regular 6 monthly reports to the HTA, and annual reports to the research ethics committee, MHRA and Co-Sponsors which will include the following:

- Programme progress
- Recruitment rate
- Drop-out rate and reasons for drop-outs
- Any ARs (NOTE SAEs will be reported annually to the Sponsor, MHRA and Research Ethics Committee)
- Financial statement

9.9 INDEMNITY

The University of Manchester will provide indemnity for non-negligent harm, subject to formal approval for the trial by The University of Manchester's Ethics Committee. Indemnity for negligent harm will be provided by the defence societies of the dentists and hygienists participating in the trial. All dentists and hygienists involved in the trial will be asked to provide evidence of current registration with a defence society.

9.10 FINANCE

Research costs will be met from a grant from the Health Technology Assessment funding stream of the National Institute of Health Research. The University of Manchester will raise contracts with the employing organisations of members of the trial team which will detail the payment schedules to reimburse costs associated with working on the trial. The research support costs will be met by Public Health Agency Research and Development. These consist of payments to practices for hosting the trial. The Department of Health, Social Services and Public Policy will arrange payments to practices through the BSO.

9.11 DATA OWNERSHIP & ACCESS

Intellectual Property Rights for this trial will be stated within the research contract between the Funder – National Institute for Health Research Health Technology Assessment (NIHR HTA) and the University of Manchester. At the end of the trial, HTA projects are published in the Monograph series, which are Crown Copyright

10 TRIAL COMMITTEES

10.1 TRIAL MANAGEMENT ARRANGEMENTS

Professor Martin Tickle will be Chief Investigator and will have overall responsibility for the project. Michael Donaldson will be Principal Investigator and responsibility for day to day management of the trial in Northern Ireland and will liaise closely with the Department of Health, Health Boards, Health Trusts, the BSO and CTU. Management of the trial manager and trial co-ordinator will be the responsibility of the Clinical Director, Community Dental Services, Northern Health and Social Care Trust. The CTU will provide training, pharmacovigilance, data monitoring and quality assure the data management processes of the trial. The York Trials Unit, through Professor Torgerson, will act as a source of advice through the duration of the trial on the design and conduct of the processes required under the regulations.

10.2 TRIAL PROJECT MANAGEMENT GROUP (TPMG)

This group will be established and will include CI, PI and operational members of the team, including members from both the CRSC and the NHSCT. This group will have responsibility for the day to day operational management of the trial and will meet monthly or bimonthly depending on the needs of the project. The discussions of the group will be formally minuted and a documented record kept in the Trial Master File.

10.3 TRIAL STEERING COMMITTEE (TSC)

This group will oversee the conduct of the trial. The TSC will be responsible for: monitoring and guiding overall progress of the trial according to the defined project timetable, monitoring scientific standards and the quality of the operational delivery; and protecting the rights and well-being of the trial participants. The TSC will be chaired independently, and will have public representation and a second independent academic. The CI, PI and co-sponsor representatives will also sit on the TSC. Observers from the HTA programme will be invited to all TSC meetings, which will take place on an annual basis, however may be convened more frequently if required.

10.4 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

This group will be chaired independently and will include a statistician, a senior paediatric dentist, a senior paediatrician and a senior NHS research manager and a representative of the public. The IDMC will monitor recruitment during the first year, AEs, baseline and outcome data collection and data quality. The IDMC can recommend that the trial stops early due to failure to recruit adequate participants, if there are serious adverse reactions, and or if logistical or data-quality problems arise that are so severe that correction is not feasible.

10.5 USER INVOLVEMENT

We will recruit and retain a pool of parents of young children from families who attend community clinics and programmes, for example Sure Start and through collaboration with Programme Managers within the HSC Research & Development Division. The trial manager will meet with the parents twice a year to update them on the trial progress, review of trial documents and to answer any questions they may have. Minutes from these meetings will be provided to the various committees of the project including the IDMC, TSC and TPMG

11 PROPOSED TRIAL MILESTONES

- Start 01.10.2009
- Site recruitment starts 01.10.2009 - ends 31.08. 2011.
- Participant recruitment and baseline examination starts 01.04.2011 - ends 30.11.2011
- Final intervention 30.11.2014.
- Outcome assessments start 01.04.2014 ends 30.11.2014.

- Close databases 31.01.2015
- Complete analysis 31.03. 2015
- Study close 30.04. 2015

12 DISSEMINATION

The results of the trial will be communicated to policy makers, the research community, NHS managers, clinicians and members of the public via a dissemination strategy. The first phase of dissemination will include reports and presentations to CDO and colleagues the Department of Health, Social Services and Public Safety, the dentists involved in the study and a short report will be distributed to parents of all participants. The second phase will include a seminar for UK policy makers organised by the team to present the results; the four UK CDOs, senior dental public health advisors and BDA, BASCD, FGDP representatives will be invited. Academic papers will be published according to CONSORT guidelines in peer reviewed, high impact journals and summaries of the research will be submitted to the British Dental Journal and Health Service Journal. Press releases will be issued to the popular media in Northern Ireland and the UK. Reports will be written for policy makers and circulated to NHS chief executives. The results will be presented at national and international conferences.

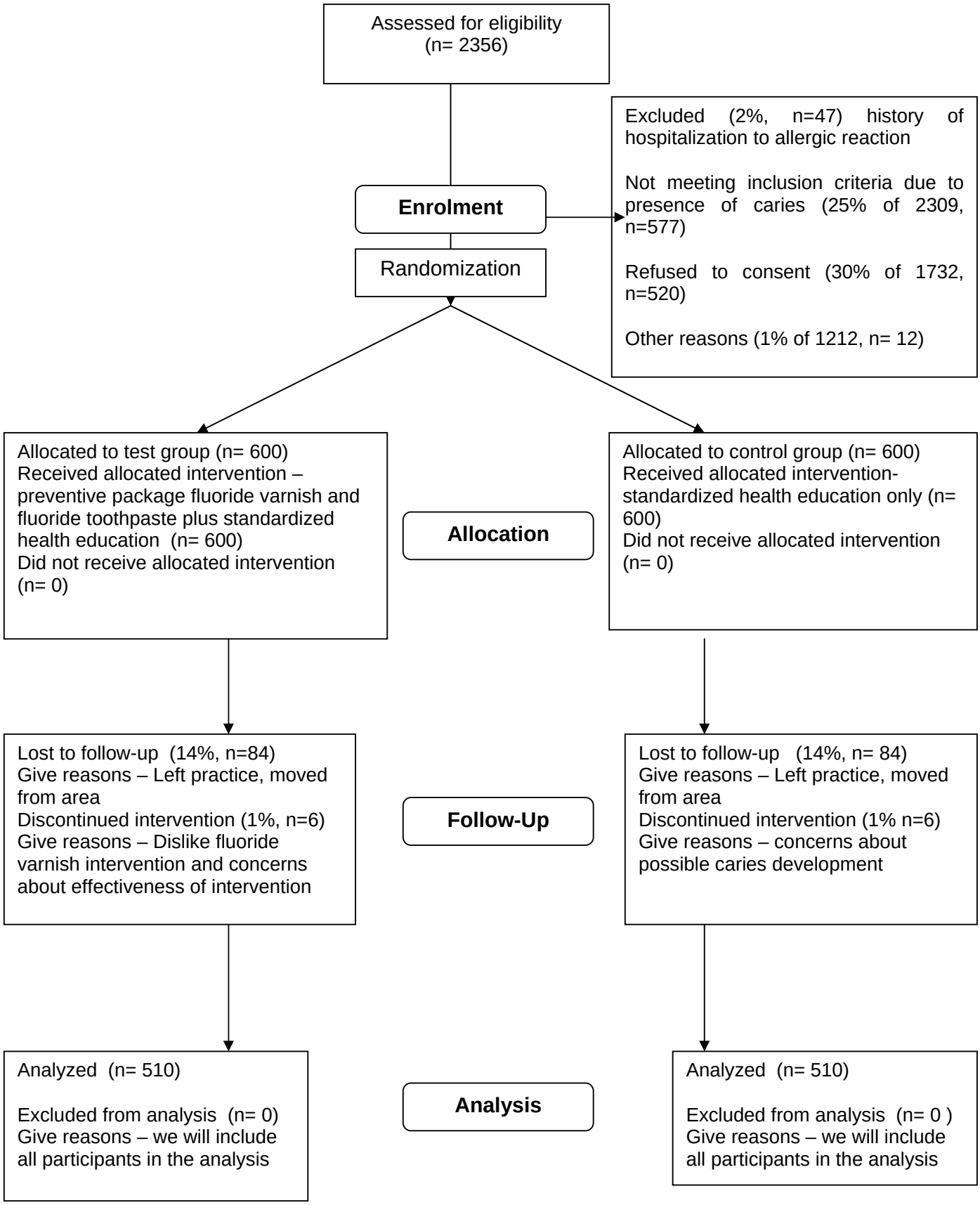
List of Appendices

Appendix I	**List of General Dental Practices that Returned a Notification of Interest and will be Considered for Enrolment of Participants.**

Church Road Dental Care	29 Church Road	Carryduff	BT8 8DT
The Village Dental Practice	33 Downpatrick Street	Crossgar	BT30 9PX
18 Dental	18 Lodge Road	Coleraine	BT52 1NB
Cushendall Dental Surgery	2 Gortaclee Road	Cushendall	BT44 0TE
Diamond Dental Clinic	7 Burn Road	Cookstown	BT80 8DL
Dental Practice	83A Bridge Street	Portadown	BT63 5AA
Algeo Dental Surgery	6 Lodge Road	Coleraine	BT52 1NB
Castlebawn Dental Practice	63 South Street	Newtownards	BT23 4JU
Bovally Dental Practice	Bovally	Limavady	BT49 0TA
Mellor Dentists	292 Shore Road	Newtownabbey	BT37 9RW
Philip Murphy & Associates	12/14 Russell Street	Armagh	BT61 9AA
Maghera Dental Care	27 Church Street	Maghera	BT46 5EA
Knock Dental Surgery	222 Knock Road	Belfast	BT5 6QD
Robert Street Dental Surgery	5 Robert Street	Lurgan	BT66 8BE
Spires Oral Care	11 Kirk Avenue	Magherafelt	BT45 6BT
Dentistry at Markethill	82 Main Street	Markethill	BT60 1PL
Shankill Dental Care	244 Shankill Road	Belfast	BT13 2BL
O'Boyle Dental Surgery	14 Trevor Hill	Newry	BT34 1DN
Dental Practice	4 Windsor Hill	Newry	BT34 1EP
Hughes O'Boyle Dental Surgery	12 Downs Road	Newcastle	BT33 0AG
Whiteabbey Dental Practice	138 Doagh Road	Newtownabbey	BT37 9QR
Bishop Street Dental Care	Bishop Street	Londonderry	BT48 6PR
Haugh Dental Surgery	5 Newcastle Street	Kilkeel	BT34 4AF
Altmore Dental Practice	61 Thomas Street	Dungannon	BT70 1HW
Camlough Dental Practice	10 Main Street	Camlough	BT35 7JG
J Mangan	13 Belfast Road	Antrim	BT41 1NY
Maine Dental Practice	14B Old Mill Park	Cullybackey	BT42 1GP
MR R H Loane	4 Hamilton Road	Bangor	BT20 4LE
Cloughoge Dental Practice	51c Forkhill Road	Newry	BT35 8QX
Dental Practice	27A Main Street	Richill	BT61 9RJ
Laura Jones & Associates	20 Broughshane Street	Ballymena	BT43 6EB
W R Elkin	8 Holmview Terrace	Campsie, Omagh	BT79 0AH
Elite Dental Care	246/248 Ravenhill Road	Belfast	BT6 8GJ
Loughside Dental Practice	214 Shore Road	Belfast	BT15 3QB
A P Gardiner	6 Henry Street	Ballymena	BT42 3AH
The Grange Dental Care	2 Crevanagh Road	Omagh	BT79 0AL
Turning Point Dental Practice	24 Barrack Street	Coalisland	BT71 4LS
Roche Dental Surgery	39 Church Street	Warrenpoint	BT34 3HN
Morgan Dental Surgery	4 Harbour Road	Kilkeel	BT34 4AR
Abercorn Dental Surgery	59 Abercorn Road	Londonderry	BT48 6TQ
Dunmurray Dental Practice	107 Kingsway	Dunmurray	BT17 9NS
Bell and Thom Dental Surgeons	17/19 Main Street	Portglenone	BT44 8AA

The Gate Lodge	554 Antrim Road	Belfast	BT15 5GJ
J D Turk	46 Cliftonville Road	Belfast	BT14 6JY
Row Valley Dental Practice	11 Irish Green Street	Limavady	BT49 9AA
Little Dental Surgery	4 Newry Road	Banbridge	BT32 3HF
Newtownstewart Dental Practice	28 Main Street	Newtownstewart	BT78 4AA
Quay	79 Ann Street	Ballycastle	BT54 6AD
M R Preston	3 Lodge Road	Coleraine	BT52 1LU
Ormeau Dental Care	324 Ormeau Road	Belfast	BT7 2GE
Cherryvalley Dental Care	33 Gilnahirk Road	Belfast	BT5 7DB
Parkash	48 Ann Street	Ballycastle	BT54 6AD
A Barkley	58 Main Street	Portglenone	BT44 8HR
E Heyes	128 High Street	Holywood	BT18 9HW
Greenisland Dental Practice	50 Station Road	Greenisland	BT38 8TP
Abercorn Dental Care	16 Newry Road	Banbridge	BT32 3HN
Bangor Dental Care	1 Moira Drive	Bangor	BT20 4RN
Dental Surgery	95 Saintfield Road	Belfast	BT8 7HN
Farquharson Dental Surgery	543 Antrim Road	Belfast	BT15 3BU
N C Dental Clinic	39 Mary Street	Newry	BT34 2AA
Moss Road Dental Health Care	112 Moss Road	Lambeg, Lisburn	BT27 4NU
Kingsway Dental Practice	230 Kingsway	Belfast	BT17 9AE
Cassidy Dental Practice	36 Kind Street	Magherafelt	BT45 6AS
Gransha Dental Surgery	89A Glen Road	Belfast	BT11 8BD
B Gibson	1 Castle Avenue	Castlewellan	BT31 9DX
Blundell & Blundell	372 Cregagh Road	Belfast	BT6 9EY
N McGale Dental Surgery	420 Falls Road	Belfast	BT12 6EN
Rossmore Dental Care	479 Ormeau Road	Belfast	BT7 3GR
Quinn Dental	53 Main Street	Randalstown	BT41 3BB
Tandragee Dental Surgery	29 Church Street	Tandragee	BT62 2AF
Castle Chambers	Castle Street	Lisburn	BT27 4XD
L D Flanagan	78 Main Street	Dungiven	BT47 4LG
Knock Dental Surgery	222 Knock Road	Belfast	BT5 6QD
Head Street Dental	40 Head Street	Enniskillen	BT74 7DB
Quayside Dental Care	87 Strand Road	Londonderry	BT48 7NN
Enlighten Dental Care	Unit 3 Cloughogue Business Park	14 Forkhill Road, Newry	BT35 8RA
Orr's Dental Surgery	9A Church Street	Banbridge	BT32 4AS
Eglington Dental Surgery	23 Cherry Drive	Eglinton	BT47 3US
York Dental Care	2 Market Place	Carrickfergus	BT38 7AW

Appendix II	**CONSORT Flowchart**



Appendix III	Declaration of Helsinki (as amended)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any SAEs. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not

in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

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