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SEAL OR VARNISH

SEAL OR VARNISH?

A RANDOMISED TRIAL TO DETERMINE THE RELATIVE COST AND EFFECTIVENESS OF PIT AND FISSURE SEALANTS AND FLUORIDE VARNISH IN PREVENTING DENTAL DECAY

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South East Wales Trials Unit
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Cardiff and Vale University Health Board

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

I. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes
1	2.0	15Jul2011	S.Hutchings
2	2.1	12Oct2011	S.Hutchings
3	3.0	24Jan2012	S.Hutchings
4	3.1	28May2012	S.Hutchings
5	3.2	NOV 2013	C.Lisles

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Section	Description of change*
IV	Changes to Trial Manager, Data Manager and Trial Administrator and contact phone numbers for Queries and SAE reporting.
7.5.2.	One spelling and typo correction.
7.6.4.	Addition of 'SAEs' into the sentence, 'The procedure for reporting SAEs/SARs is described in Section 8.4.'
8	SAE – update to whole section following changes to SEWTU Operating Procedures in relation to SAE reporting.
8	Delton and Duraphat changed to Delton® and Duraphat® where absent.

*Please note – all of these are non-substantial amendments.

STATEMENT OF COMPLIANCE

General Information This protocol describes the *Seal or Varnish* clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but centres entering patients for the first time are advised to contact the South East Wales Trials Unit (SEWTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to the South East Wales Trials Unit.

Compliance This trial will adhere to the conditions and principles which apply to all clinical trials as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, EU Directive 2001/20/EC, EU Directive 2005/28/EC and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), as amended, the Research Governance Framework for Health and Social Care (Welsh Assembly Government 2nd Edition, September 2009 and Department of Health 2nd Edition, July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding The Seal or Varnish trial is being funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) program (Ref. 08-104-04).

II. SIGNATURE PAGES

Protocol Approval

The signatures below constitute the approval of this protocol, and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, and according to international Good Clinical Practice principles (ICH-GCP), in addition to local legal and regulatory requirements.

Prof. Ivor Chestnutt	Co-Chief Investigator		21/1/14
Name	**Role:**	**Signature**	**Date**
			21/1/14
Prof. Barbara Chadwick	Co-Chief Investigator		21/1/14
Name	**Role:**	**Signature**	**Date**
Prof. Kerenza Hood	SEWTU Director		20/1/14
Name	**Role**	**Signature**	**Date**

III. SYNOPSIS

Study Title	Seal or Varnish? A Randomised Trial To Determine The Relative Cost And Effectiveness Of Pit And Fissure Sealants And Fluoride Varnish In Preventing Dental Decay
Sponsor ref.	SPON766-09
Clinical Phase	IV
Trial Design	Randomised, assessor-blinded, two-arm, parallel group trial in 6-7 year old schoolchildren. Clinical procedures and assessments will be performed at primary schools in South Wales via the use of a mobile dental clinic.
Trial Participants	Male and female 6-7 year old schoolchildren attending 'Community First' Schools (as designated by Welsh Assembly Government) in South Wales, UK
Planned Sample Size	920 (460 per arm)
Number of sites	1 mobile dental clinic covering approximately 65 schools
Follow-up duration	3 years from first IMP administration
Planned Trial Period	4.5 years (from first patient consent to last assessment)
Objectives	*Primary:* To compare the clinical effectiveness of Pit and Fissure Sealants (PFS) and Fluoride Varnish (FV) in preventing dental caries in first permanent molars in 6-7 year-olds, as determined by: • The proportion of children developing caries on any one of up to four treated first permanent molars • The number of treated first permanent molar teeth caries-free at 36 months *Secondary:* • To establish the costs and budget impact of PFS and FV delivered in a community/school setting and the relative cost-effectiveness of these technologies • To examine the impact of PFS and FV on children and their parents/carers in terms of quality of life/treatment acceptability measures. • To examine the implementation of treatment in a community setting with respect to the experience of children, parents, schools and clinicians.
Outcome Measures	*Primary:* The primary outcome measure will be the development of dental caries in first permanent molars at 36 months *Secondary:* Cost-effectiveness outcome measures Costs to the NHS for each technology will be determined at baseline, 12 months, 24 months and 36 months in conjunction with relevant dental and finance staff and will account for time taken for treatments, clinic and staff involvement, materials and equipment (to be logged and costed using published unit costs). The costs for children and their families will be determined from questionnaires completed during the treatment phase. The costs to participating schools will be

	derived via semi-structured interviews conducted with staff from participating schools. Potential costs of treatments avoided will also be determined. The relative cost-effectiveness will be estimated by integrating the clinical and cost effectiveness. In addition, utility values will be measured as Quality Adjusted Tooth Years (QATYs). Health related quality of life (QoL) scores will be determined at 12 months, 24 months and 36 months using the Child Health Utility 9D (CHU-9D) questionnaire. These scores will be mapped onto utility scores to generate Quality Adjusted Life Years (QALYs). Treatment Acceptability outcome measures A modified version of the Delighted-Terrible Faces Scale will be used to determine patient acceptability. This will be triangulated via a series of semi-structured interviews with children, parents, school staff and clinical personnel on treatment acceptability. Acceptability of the clinical placement of the technologies under investigation from the perspective of dental staff will be assessed using observational scales, and the following indicators of patient acceptability/adverse outcomes will be recorded: vomiting, crying, gagging, excessive arm/leg movements and other signs of distress. A sample of non-participating parents and parents who withdraw their children from the trial will be invited to partake in an interview to determine reasons for non-participation/withdrawal.
Investigational Medicinal Products	• Pit and Fissure Sealant: Delton® Light Curing Pit & Fissure Sealant (Dentsply Ltd; CE0086), supplied as 2.7 ml bottles for multiple applications. Applied topically as a thin layer to occlusal surface of eligible teeth at 0 months and re-applied (only if required) at 6, 12, 18, 24, and 30 months. • Fluoride Varnish: Duraphat® 50 mg/ml dental suspension, (Colgate-Palmolive (UK) Ltd; PL 00049/0042), supplied as 10 ml tubes for multiple applications. Applied topically as a thin layer to occlusal surface of eligible teeth at 0, 6, 12, 18, 24, and 30 months. As per SmPC, dosage per single application will not exceed 0.4 ml.

IV. CONTACT DETAILS

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<<Please contact the Trial Manager for general queries and supply of trial documentation>>

Randomisation:

Randomisation

A randomisation list for each school will be produced by SEWTU and provided to the Mobile Dental Clinic

(See Section 5.8 for more details)

Clinical Queries:

Clinical Queries

All clinical queries should be directed to the Trial Manager (02920 687931) who will direct the query to the most appropriate clinical person

Serious Adverse Events (SAE)

SAE reporting

Where the adverse event meets one of the serious categories an SAE form should be completed by the investigator (or suitable delegate) and faxed to the Seal or Varnish Trial Manager **(Tel: 02920 687931)** within 24 hours of becoming aware of the event.

(See Section 8 for more details)

Fax Number: 02920 687612

V. TABLE OF CONTENTS

VI. GLOSSARY OF ABBREVIATIONS

ACRPH	Applied Clinical research and Public Health, Cardiff University School of Dentistry
AE	Adverse Event
AR	Adverse Reaction
BSPD	British Society of Paediatric Dentistry
CDS	Community Dental Service
CHU-9D	Child Health Utility 9 Dimension questionnaire
CI	Chief Investigator
CRC Cymru	Clinical Research Collaboration for Wales
CRF	Case Report Form
CTA	Clinical Trials Authorisation
EudraCT	European Clinical Trials Database
FPM	First Permanent Molar
FV	Fluoride Varnish
GCP	Good Clinical Practice
GDP	General Dental Practitioner
HE	Health Economics
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IC	Informed consent
ICDAS	International Caries Detection and Assessment System
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
MDC	Mobile Dental Clinic
MHRA	Medicine and Healthcare products Regulatory Agency
NHS	National Health Service
Parent	Person(s) with parental responsibility
PI	Principal Investigator
PIS	Patient Information Sheet
PFS	Pit and Fissure Sealant
QALY	Quality-adjusted Life Years
QoL	Quality of Life

R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SEWTU	South East Wales Trials Unit
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
SMPU	St Mary's Pharmaceutical Unit
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMG	Trial Management Group
TSC	Trial Steering Committee
WHO	World Health Organisation
UHB	University Health Board

1. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1.1. Trial Site and Investigator Team

The study will be performed at eligible primary schools in South Wales, with all study procedures and assessments conducted within a mobile dental clinic (MDC) coordinated by the Cardiff and Vale University Health Board Community Dental Service (CDS). The MDC will be considered the study site for the purpose of the trial, and will be under the responsibility of the Principal Investigator (PI). The overall responsibility for the study will rest with the Co-chief Investigators, Prof I Chestnutt and Prof B. Chadwick. The trial manager will act on behalf of the Co-chief Investigators to ensure the smooth and efficient running of all aspects of the study.

Co-investigators providing clinical and scientific expertise into the trial, together with the trial management team are detailed in Section IV. The PI will delegate study related activities to appropriate trained and qualified personnel according staff responsibilities and job descriptions. This will be documented in a study specific Delegation of Responsibilities form.

1.2. Trial sponsorship and Indemnity

The proposed study will be coordinated by the UK Clinical Research Collaboration (CRC) registered SEWTU, Cardiff University Medical School and the Applied Clinical Research and Public Health Group (ACRPH), Cardiff University Dental School.

Cardiff University will act as Sponsor and will provide indemnity and compensation in the event of a claim by, or on behalf of participants, for negligent harm as a result of the study design and/or in respect of the protocol authors/research team. Cardiff University does not provide compensation for non-negligent harm.

All amendments, substantial and non-substantial, will receive approval from Cardiff University (in addition to the REC, NHS R&D and MHRA, as required; see Section 10.1.2).

The study will be conducted in accordance with SEWTU generic and study-specific operating procedures (SOPs) and Work Instructions. All study related staff will be trained in those aspects of Good Clinical Practice (GCP) appropriate to their role in the study. CDS staff will be trained in appropriate aspects of GCP (in particular, the informed consent process). The trial manager will regularly visit the study site (i.e. the MDC) to review compliance with the study protocol.

All applicants and clinical staff employed in a role that affects patient care will hold clinical contracts with the Cardiff and Vale University Health Board, conferring the protection of the NHS clinical negligence arrangements for staff. The Chief Investigators hold honorary consultant clinical contracts with the Cardiff and Vale University Health Board and therefore are also protected by NHS clinical negligence arrangements.

All participants will be treated at the MDC, which is considered part of an NHS site; therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants.

2. TRIAL SUMMARY & SCHEMA

2.1. Trial summary

'Seal or Varnish' is an individually randomised, assessor-blinded, two-arm, parallel group trial that aims to identify and compare the relative clinical and cost-effectiveness of pit and fissure sealant (PFS) and fluoride varnish (FV) for the prevention of dental caries in first permanent molar teeth in 6-7 year old school children.

The trial will utilise the infrastructure and resources established by the current Cardiff and Vale UHB Community Dental Service (CDS) 'Designed to Smile' programme. Eligible children attending primary schools in 'Communities First' areas (as designated by the Welsh Assembly Government) in South Wales will be randomised to receive either PFS or FV following a baseline assessment by a suitably qualified and calibrated dentist who will also prescribe the treatment. Following randomisation, treatment will be provided by a dental hygienist according to the appropriate conventional CDS clinical protocol (Appendices 1 & 2). Participants will be re-examined by the calibrated dental examiner annually. Hygienists will visit every six months for three years. At these visits sealant retention will be checked and reapplied/topped up if deficient or FV re-applied (subject to treatment allocation).

The primary outcome measures are:

- To establish the relative clinical-effectiveness of the two treatments (PFS and FV).
- To establish the relative cost-effectiveness of the two treatments (PFS and FV).

The secondary outcome measures of the trial are to assess patient acceptability through the use of scales/questionnaires completed by children and clinicians, and through interviews. Patient acceptability will be compared by trial arm.

A process evaluation will also be carried out, using interview data, to investigate how the intervention is conducted and received by clinicians, schools, parents and children in order to determine factors affecting how the treatment is implemented in a community setting. This will include a longitudinal component of exploring how the treatment and its reception by various groups changes over time.

Non-participating parents will also be interviewed to ascertain reasons for non-response or non-consent, implications of this for programme implementation, and any impact this may have for bias in the study.

Further details regarding the outcome measures for the study are described in Section 9.1.

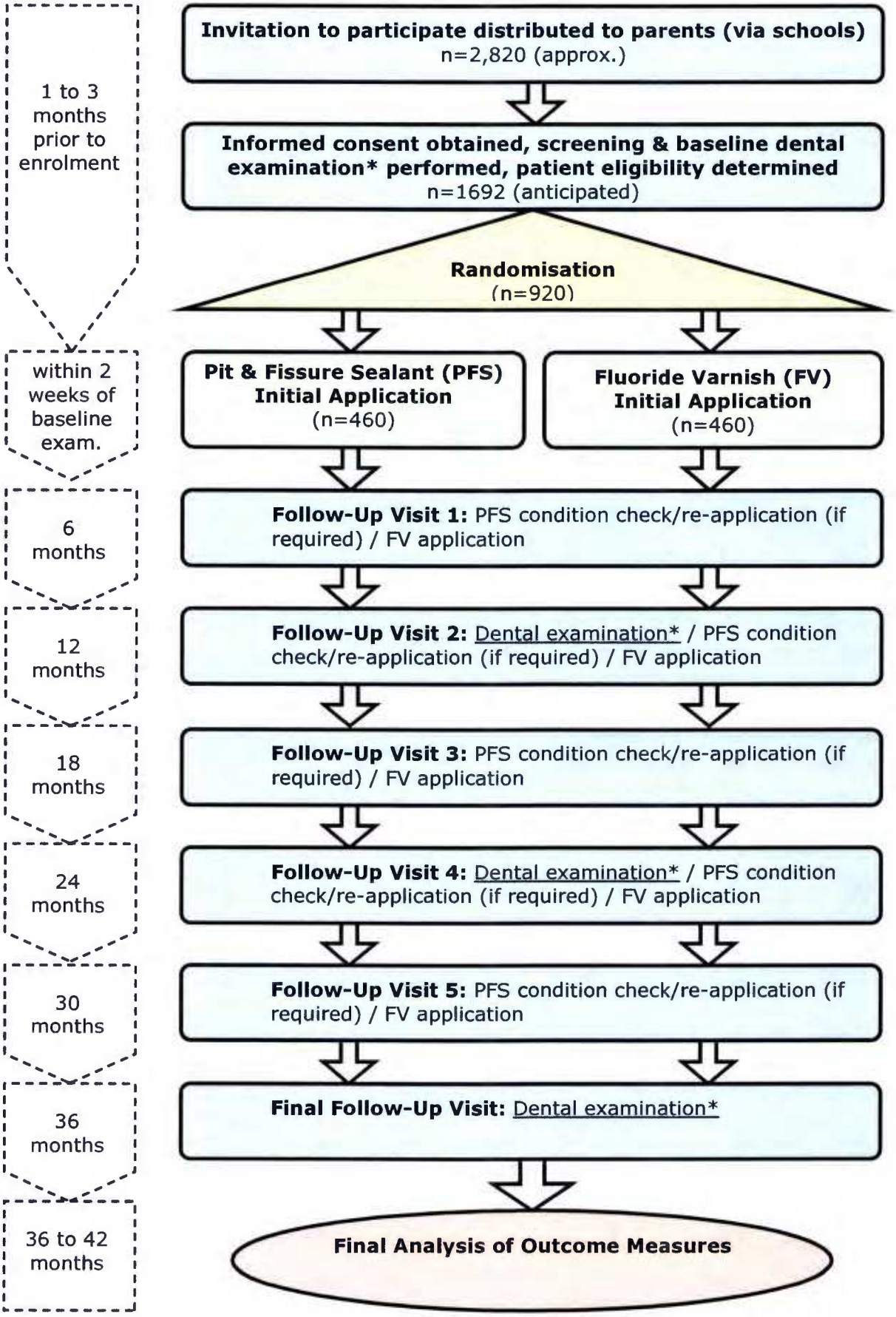
2.2. Trial schema

The schedule of events for the trial is summarised in Figure 1. Full details of assessments performed (clinical and non-clinical) are presented in Section 7.

2.3. Participant flow diagram

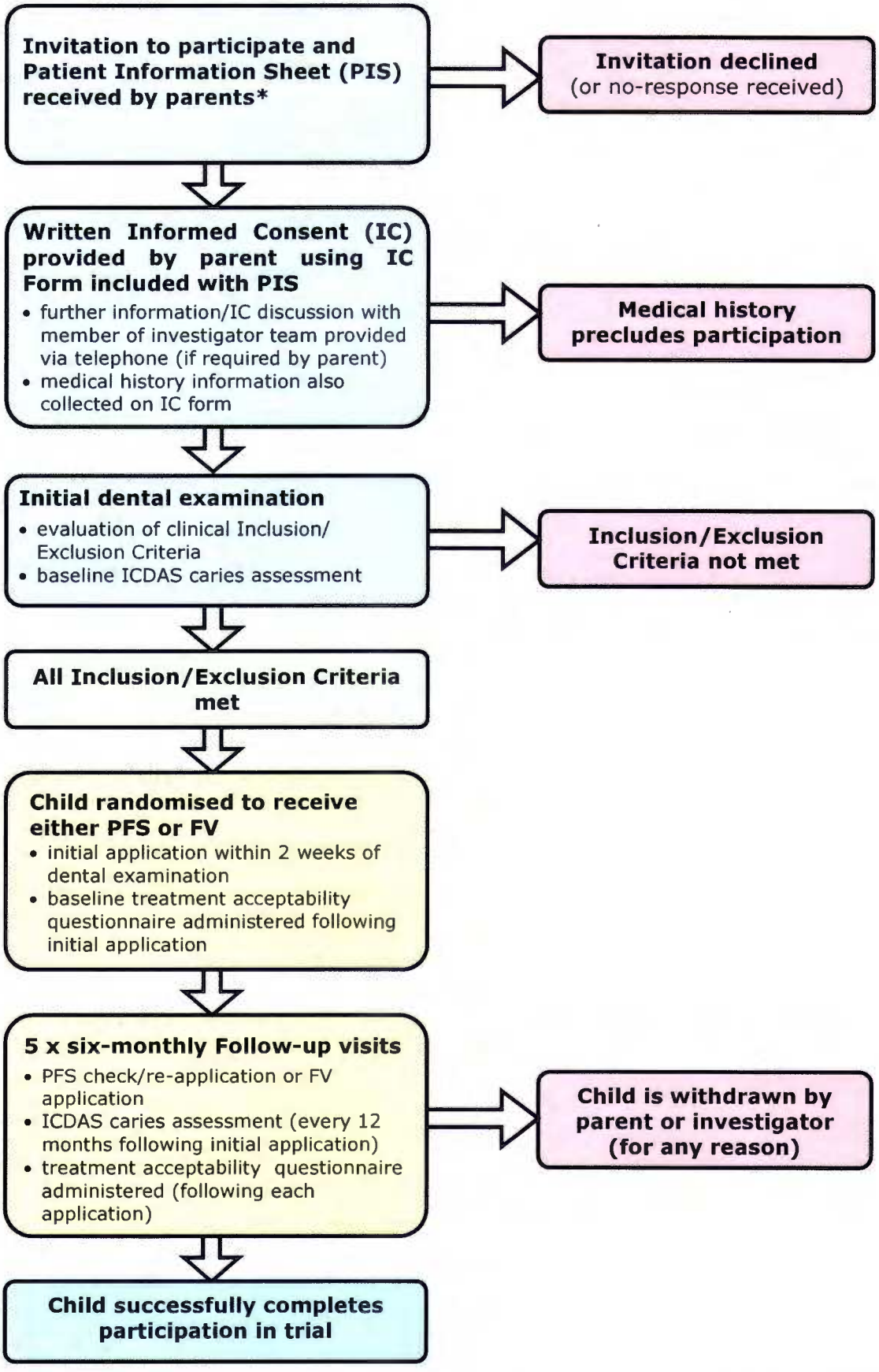
A flow diagram summarising how participants will progress through the trial is presented in Figure 2.

Figure 1 - Trial Schema



*Includes ICDAS caries assessment

Figure 2 - Participant flow diagram



*or person with parental responsibility

3. INTRODUCTION

3.1. Background

Despite the decline in the prevalence of dental decay in the United Kingdom in the last three decades, 57% of 15 year-olds still have dental caries (tooth decay) sufficiently severe to require a filling or extraction (Pitts *et al.*, 2006). Dental caries is uneven in its distribution in the population and has been shown by numerous studies to be closely linked to socioeconomic deprivation (Locker, 2000), with a three-fold difference in disease burden from most to least deprived (Sweeney *et al.*, 1999). Within the mouth, the majority of detected incremental decay is to be found on the pit and fissure surfaces of molar teeth in children (Chestnutt *et al.*, 1996) and adults (Hopcraft *et al.*, 2006). These facts dictate the need for caries-prevention technology, targeted at the most susceptible tooth surfaces in the most susceptible members of the population. Two competing technologies have the potential to fulfil this role, pit and fissure sealants and fluoride varnishes.

3.1.1. Pit and fissure sealant

Pit and fissure sealants comprise a Bis-GMA resin, which is applied to the occlusal surface of the tooth using acid-etch technology. They work by physically obliterating the pit and fissure system which harbours cariogenic organisms and thereby inhibit the initiation of caries. First developed in the 1960s, they are an established technology and widely used in clinical practice. Numerous studies have investigated the clinical effectiveness of fissure sealants and this has been the subject of a recent Cochrane review. A meta-analysis of seven studies comparing sealed teeth to untreated controls demonstrated caries reductions ranging from 87% at 12 months to 60% at 48-54 months (Ahovuo-Saloranta *et al.*, 2008).

3.1.2. Fluoride varnish

Fluoride varnishes have also been marketed since the 1960s and comprise a topical medication which is painted onto the tooth surface. They contain a high concentration of fluoride (22,600 ppm) and are licensed for application by dental professionals. The varnish forms a quick-setting base which subsequently releases fluoride. Fluoride acts to prevent caries by inhibiting the demineralisation and encouraging the remineralisation of dental enamel. A Cochrane review suggested a pooled prevented fraction estimate of 46% (95%CI 30%-63%) when fluoride varnish is tested against no treatment controls (Marhino et al., 2002).

3.1.3. Cost-effectiveness of technologies

In relation to the cost-effectiveness of technologies in this field the evidence base is generally sparse with relatively few attempts to assess the relative worth of techniques to prevent dental decay. Those that have been undertaken tend to suffer from design and methodological flaws. However, one US study (Bhuridej et al, 2007) assessed the 4-year incremental cost-utility of sealing first permanent molars, compared with non-sealed molars, of 6-year olds from a societal perspective and identified the group of teeth or children in whom sealants are most cost-effective. They concluded that sealants improved overall utility of first

permanent molars after 4 years; that the cost-utility ratio of sealing the first permanent molar varied by arch and type of utilisers; and that sealing first permanent molars in lower dental utilisers was the most cost-effective approach for prioritizing limited resources. However, this study was a comparison between sealing and non-sealing, as opposed to a comparison between different preventive technologies. Thus, while the clinical effectiveness of the technologies (PFS and FV) as caries-preventive measures is established when compared to no treatment controls, a significant question remains unanswered: What is the relative clinical and cost-effectiveness of these technologies?

The application of PFS in particular is an involved procedure, the success of which is dependent on clinical delivery in a dental-chair. The acid-etch necessary for their long-term adherence to the tooth surface is critically dependant on maintaining a dry-field during application. The clinical technique involves the use of rotary dental instruments to clean the tooth surface, suction devices and a compliant patient. In contrast, FV application simply involves drying the tooth and painting with a brush/applicator. FV can be applied by less skilled dental personnel (nurses) whereas PFS requires the involvement of a dentist or dental hygienist. If FV were proven to be an acceptable alternative to PFS (in terms of clinical, cost and patient acceptability criteria) then the potential benefits to the NHS in terms of health improvement and the effective and efficient delivery of services would be enormous.

3.2. Rationale for current trial

Preventive dental methods can be very effective in reducing tooth decay in children. A recent Cochrane review has compared the effectiveness of pit and fissure sealants with fluoride varnishes in the prevention of dental decay on occlusal surfaces (Hiiri et al 2010). Hiiri and colleagues concluded that while there was some evidence of the superiority of PFS over FV in occlusal decay prevention it remains unclear to what extent there is a difference between the effectiveness of PFS and FV. Importantly from the perspective of the NHS, there is insufficient evidence on which to make recommendations for clinical practice and which (PFS or FV) represents the most effective technology. The review did not specifically address the relative efficiency of the technologies.

We therefore believe that there is good quality secondary research evidence which has identified the need for the proposed work. Determination of the posed research question will be of great value to the NHS.

From a societal perspective, the cost of treating dental caries poses a substantial burden on the NHS and individuals throughout life. Avoiding the pain and suffering associated with dental caries is desirable, as is avoiding the impact of dental disease on the quality of life of affected individuals. Dental restorations in permanent teeth in childhood require maintenance throughout life. The outcome of this trial has the potential to benefit both those participating and, by extrapolation, the one in three children in Great Britain who have experienced dental decay by eleven years of age.

4. TRIAL AIMS AND OBJECTIVES

4.1. Trial Aim

The overall aim of the study is to identify and compare the relative clinical and cost-effectiveness of two established technologies, pit and fissure sealants (PFS) and fluoride varnish (FV) for the prevention of dental caries in first permanent molar teeth in children aged 6-7 years.

4.2. Trial Objectives

4.2.1. Primary objective

To compare the clinical effectiveness of PFS and FV in preventing dental caries in first permanent molars in 6-7 year-olds, as determined by:

- The proportion of children developing new caries on any one of up to four treated first permanent molars
- The number of treated first permanent molar teeth caries-free at 36 months

4.2.2. Secondary objectives

- To establish the costs and budget impact of PFS and FV delivered in a community/school setting and the relative cost-effectiveness of these technologies
- To examine the impact of PFS and FV on children and their parents/carers in terms of quality of life/treatment acceptability measures.
- To examine the implementation of treatment in a community setting with respect to the experience of children, parents, schools and clinicians.

5. INVESTIGATIONAL PLAN

5.1. Overall Trial design

This is a phase IV randomised, assessor-blinded, two-arm, parallel group trial in 6-7 year old children. A total of 920 participants will be randomised to receive either PFS or FV. Clinical procedures and assessments will be performed at approximately 65 schools in South Wales via the use of a mobile dental clinic.

The target population is Year 2/3 children (aged 6-7 years) attending primary schools in designated Communities First areas. All children in these schools are deemed at high caries-risk according to Scottish Intercollegiate Guidelines Network (SIGN)/British Society of Paediatric Dentistry (BSPD) guidelines (SIGN, 2000; Nunn et al., 2000) and qualify for PFS/FV application. With parental consent and child assent, children aged 6-7 years who have at least one erupted non-carious first permanent molar tooth will be randomly allocated to receive either PFS or FV.

Data entry, management and analysis will be conducted centrally at SEWTU. Data will be analysed following the intention-to-treat (ITT) principle.

5.1.1. Clinical Evaluation

Participants will undergo a clinical examination using standard visual caries diagnosis (both enamel and dentinal level) at baseline and 12, 24 and 36 months by a trained and calibrated dentist, blind to treatment allocation. All fully-erupted non-carious first permanent molars (FPM) will be treated. Children randomised to receive PFS will have sealant applied at baseline (and on subsequent newly-erupted FPM during the course of the trial) and reviewed/repaired at 6 monthly intervals. Children randomised to receive FV group will receive varnish applications at 6 monthly intervals. Participants who do not have at least one fully-erupted and non-carious FPM at baseline will be excluded. Parents of children who are eligible for inclusion but who also have carious FPM or primary teeth will, in line with current clinical practice, be informed and offered treatment within the CDS. Where children enrolled onto the study are registered with a General Dental Practitioner (GDP), the GDP will be informed of the child's participation in the study and requested to not apply either PFS/FV (or other fluoride-based treatment) for the duration of the trial.

5.1.2. Health Economics Evaluation

The assessment of relative cost-effectiveness of PFS and FV will be undertaken from the perspectives of the health service, patients and their families and society in general. Thus data will be collected relating to the costs associated with the provision of pit and fissure sealants and fluoride varnish by a variety of methods: postal questionnaires (Appendix 3) to family members to obtain estimates of travel costs and productivity costs; semi-structured interviews with key relevant dental and finance staff to obtain profiles of treatment costs; questionnaires for school head teachers to ascertain resource implications of providing the service for the participating schools; and analysis of documents and price lists to derive costs of materials and equipment. In addition, the impact of the treatment on

health-related quality of life (HRQoL) of children will be assessed using the Child Health Utility 9 Dimension (CHU-9D; Stevens, 2009) questionnaire (Appendix 4). Data relating to the effectiveness will be obtained from the proposed primary and secondary outcome measures utilised throughout the trial and from the outcome measures that will enable the cost-utility analysis to be conducted.

The budget impact of each of the technologies will be determined by the costs relating specifically to the health service and will include an estimate of treatments etcetera avoided as a result of a reduction in dental caries over a 1-year and 3-year perspective. Longer time horizons may be considered if justified from the data collected.

5.1.3. Evaluation of Treatment Acceptability and Process Evaluation

Treatment acceptability will be measured primarily by a modified version of the Delighted-Terrible Faces Scale (Andrews and Withey, 1976; Marshman and Hall, 2008; Appendix 5). During the clinical placement of the technologies under investigation, the indicators of patient acceptability/adverse outcomes: vomiting, crying, gagging, excessive arm/leg movements and other signs of distress (Hawkins et al, 2004) will be recorded by both the dental hygienist and dental nurse using an observational scale (Appendix 6). These scales will be triangulated with each other and data will also be triangulated with parent and child interviews which will include questions about treatment acceptability. Children and their parents from each trial arm will be interviewed in order to compare the experience of PFS and FV treatment.

A process evaluation of the trial will also be conducted through interviews of children, parents, school staff and clinicians. Each group of child and parent interviewees in both trial arms will be purposively sampled for a maximum difference of children's acceptability ratings within each group to ensure a range of responses to treatment is captured. The sample size will be 48 children - 24 in each trial arm - plus one parent of each child, totalling 48 parents. Interviews will also explore change over time with respect to how the programme is implemented by schools and providers, contextual factors affecting the programme, how parents and children respond to the intervention and the acceptability of participating in the trial aspect of the programme.

Potential bias will be investigated through interviews with 20 parents who do not consent to the treatment and 20 do not respond to requests for participation. Parents will be interviewed about reasons for non-participation and profiles of non-participating parents and their associated school will be analysed to investigate any common factors in those parents.

5.2. Discussion of Trial Design

The study will be conducted in primary schools in South Wales. Under the umbrella of the Welsh Oral Health Action Plan, the Community Dental Service (CDS) in Cardiff and Vale University Health Board delivers a primary school based PFS placement programme ('Designed to Smile') to approximately 3,300 6 year-olds annually. This programme and its predecessor has been in place since 2002. The programme involves Community First Schools, so designated by the Welsh

Assembly Government on the basis of the high socioeconomic deprivation status of the school catchment area. The prevalence of dental caries in these areas is amongst the highest in the United Kingdom (BASCD, 2007). Permission to adapt the Designed to Smile programme for the purposes of this trial has been granted by the Chief Dental Officer for Wales.

A schools-based programme, utilising mobile dental clinics, is considered to have several advantages over conducting the proposed research in general dental practices. The Designed to Smile programme is established and gives access to a cohort of high-risk children, experiencing the necessary burden of disease to allow an appropriate test of the technologies. This setting accesses children who might not otherwise routinely attend a general dental practice - attendance being linked to socioeconomic status (Morris et al., 2004). In addition to having the necessary throughput of patients to achieve the required recruitment rate of at-risk children (as defined by BSPD / SIGN guidelines), a schools-based setting will facilitate control over retention and follow-up. Furthermore, and perhaps most importantly, the CDS has established a relationship with the schools, parents and the children over many years which will obviously facilitate meaningful user and participant involvement in the study. In addition to service user representatives (i.e. parents of year 2 school children in South Wales), staff involved in the existing CDS programme have been consulted during the design and work-up of this trial, ensuring that it will be implemented and conducted in a way that is empathetic to the needs of the participating children, their parents and their schools.

On the basis that we are testing the relative clinical and cost-effectiveness of two established technologies, both of which have been proven clinically effective against placebo treatments (Marhino et al. 2002; Ahovuo-Saloranta et al. 2008), this trial will not contain a placebo control arm.

5.3. Centre selection

As detailed in Section 1, all study procedures and assessments will be conducted within a mobile dental clinic (MDC) coordinated by the Cardiff and Vale University Health Board CDS, and therefore for the purpose of the trial the MDC will be considered the study site. The MDC is already being used to implement the 'Designed to Smile' Programme.

The trial will be conducted using the MDC within the school grounds of approximately 65 'Community First' Primary Schools in South Wales. Criteria for selection of these schools, is based on these schools being designated 'Community First' Schools by the Welsh Assembly Government, on the basis of the high socioeconomic deprivation status of the school catchment area.

The following documents are required to be completed and returned to SEWTU before the MDC can commence recruiting children from any school:

Documents Cardiff & Vale UHB CDS complete and return to SEWTU

- Completed Signature List and Roles and Responsibilities document
- Completed contacts list of all site personnel working on the Study

- Signed Subcontract between Cardiff & Vale UHB CDS and Cardiff University
- A copy of the NHS R&D approval for the study

Documents school complete and return to SEWTU

- A signed Study Agreement between School and SEWTU

Upon receipt of all the above documents, the Seal or Varnish Trial manager will send a confirmation letter to CDS detailing that the Seal or Varnish MDC team is now ready to recruit patients into the trial. This letter must be filed in the MDC Trial Site File. Along with this confirmation letter, the MDC should receive a study pack holding all the documents required to recruit a patient into the 'Seal or Varnish' Trial.

5.4. Participant selection

Children will be considered eligible to join the trial if they meet all of the following inclusion criteria and none of the exclusion criteria. Certain inclusion and exclusion criteria (where identified) require evaluation by a dentist during a baseline clinical examination. Only children that are considered to meet all other inclusion/exclusion criteria will undergo a baseline clinical examination.

5.4.1. Inclusion criteria

- Children aged 6-7 years, attending the schools participating in the current Cardiff and Vale UHB Designed to Smile Programme
- Children for whom the person with parental responsibility has provided written informed consent
- Children with at least one fully-erupted caries-free first permanent molar (**determined at baseline examination**)

5.4.2. Exclusion criteria

- Children whose medical history precludes inclusion (i.e. those with a history of hospitalisation for asthma, or severe allergies, or allergy to Elastoplast; **determined from Medical History Form completed by parents**)
- Children with known sensitivity to colophony (kolophonium), or any of the product ingredients (e.g. methylacrylate in PFS; **determined from Medical History Form completed by parents**)
- Children with ulcerative gingivitis or stomatitis (**determined at baseline examination**)
- Children with any facial or oral infections e.g. cold sores (**determined at baseline examination**)
- Children with any abnormality of the lips, face or soft tissues of the mouth that would cause discomfort in the provision of PFS/FV (**determined at baseline examination**)

- Children who are showing obvious signs of systemic illness (e.g. colds, 'flu, chicken pox etc) (**determined at baseline examination**)
- Children currently participating in another clinical trial involving an investigational medicinal product (IMP; **determined from Medical History Form completed by parents**).

5.5. Recruitment

5.5.1. Number of participants

It is planned to recruit 920 participants to be randomised equally (460 per arm) to the two technologies investigated in this trial. The statistical justification for this number is discussed in Section 9.3. Where possible, information will be provided and consent sought from parents prior to the end of the preceding school year[1].

5.5.2. Recruitment of schools

Eligible schools currently involved in the Cardiff and Vale UHB CDS Designed to Smile programme will be invited to participate in the trial. Schools that express interest in participating will be visited by the trial management team to discuss practical/logistical aspects of the trial and, if applicable, agreement to participate in the trial will be documented.

5.5.3. Recruitment of participants

In line with the current procedures for informing parents of children of the existing Designed to Smile programme, invitation packs to parents for their child's participation in the trial will be distributed in class by teachers for the child to take home.

The following documents will be included in the invitation packs:

- Patient Information Sheet (PIS) for parents
- Medical History Form
- Informed Consent Form (ICF)

5.6. Informed consent

The Patient Information Sheet (PIS) included in the Seal or Varnish invitation pack will introduce the trial to the parents and ask the parent to take the time to read the PIS before deciding whether or not they wish for they and their child to participate in the trial. Parents will also be informed of the option for their child to enter the existing Designed to Smile programme instead of the trial. Explicit in the PIS will be the opportunity to discuss any aspect of the trial with a member of the Investigator team via the telephone. A dedicated phone number for this purpose will be provided, with the provision for parents to leave a telephone number and email address to be contacted by a member of the Investigator team

[1] The original aim was to recruit all participants within one school year, however recruitment during the first school year did not reach the target of 920; for this reason, the decision to extend recruitment to a second cohort from the next school year was made by the Trial Management Group (supported by the Independent Data Monitoring Committee, Trial Steering Committee and trial funder [NIHR]).

at the next available opportunity. Parents will also be asked to discuss the trial with the child.

After considering the information provided in the Seal or Varnish invitation pack, and discussing the trial with a member of the Investigator team (if so required) parents wishing for their child to participate will be asked to sign and date the ICF. The parent will also be asked to confirm on the ICF if they have had the opportunity to discuss the trial with a member of the trial team, or alternatively, if they do not require any further information to make a decision regarding their child's participation. Parents will also be asked to confirm if they wish their child to enter the current Designed to Smile programme if ineligible for the trial.

The parent will be asked to complete the Medical History Form in order for relevant medical and dental information to be collected to allow the Investigator to determine the child's eligibility for the trial. Confirmation that the child is not currently participating in another clinical trial involving an IMP will also be obtained on the Medical History Form.

An envelope addressed to the Seal or Varnish MDC team will be included in the invitation pack for the parent to enclose the ICF and Medical History Form. As is standard practice in the current Designed to Smile programme, the envelope will be given to the child to return to their class teacher. Upon receipt of the ICF and Medical History Form, a designated member of the Seal or Varnish MDC team will liaise with an appropriate member of school staff to verify the name and signature on the ICF is in agreement with the school's records regarding the persons with parental responsibility for that child.

5.7. Clinical Screening/Baseline Dental Examination

Children for whom parents/persons with parental responsibility have provided written informed consent, and whose medical history does not preclude participation, will undergo a clinical dental examination to determine eligibility based on the clinical inclusion and exclusion criteria.

Children who are considered by the Investigator to meet all inclusion criteria and no exclusion criteria following the clinical dental examination will be confirmed eligible for randomisation, and will undergo a baseline ICDAS caries assessment.

Where a participant has no fully-erupted caries-free first permanent molar teeth, but meets all other inclusion/exclusion criteria, the child may be undergo a second clinical screening/baseline examination at a later date (which may extend into the subsequent school year). In such cases the parent will receive a letter via the CDS confirming that the MDC will be returning to the child's school for additional baseline examinations, requesting that the parent contacts the study team if they no longer wish for their child to participate in the trial. In addition the parent will be asked to notify the CDS (via a Medical History Update Form enclosed with the letter) if there has been any change in the child's medical history since the parent returned the original Medical History Form.

Following the clinical dental examination the child will be given a letter to take home to their parent/guardian communicating the following information depending on the outcome of the examination:

- That their child is suitable to be included in the study and that they will be receiving treatment in the next 2 to 4 weeks. The letter will also advise parents not to give their children any fluoride-containing dental medication (tablets, gels etc) other than their normal fluoride toothpaste (if used) for the duration of the trial.
- That their child is not suitable for the trial. If applicable, parents will also be informed if the child is eligible for the existing Designed to Smile programme.

Regardless of the child's eligibility for enrolment into the trial, if it is identified during the clinical dental examination that the child requires additional treatment to one or more teeth, this will also be communicated to the parent via the above forms. The parent will be advised that the treatment may be provided though the CDS (for which they will need to provide consent using an additional enclosed treatment consent form), or to make an appointment with their GDP if preferred.

In instances where a parent returns the ICF and Medical History Form after the baseline examinations have taken place for that school, the participant may be screened for enrolment onto the study at a later date (which may extend into the subsequent school year). In such cases the parent will receive a letter via the CDS confirming that the MDC will be returning to the child's school for additional baseline examinations, requesting that the parent contacts the study team if they no longer wish for their child to participate in the trial. In addition the parent will be asked to notify the CDS (via a Medical History Update Form enclosed with the letter) if there has been any change in the child's medical history since the parent returned the original Medical History Form.

5.8. Randomisation and unblinding

Randomisation will be coordinated centrally by SEWTU. Randomisation lists will be produced for each school by a SEWTU statistician following input of relevant data from screening/baseline examination case report forms (CRFs), and provided to the MDC team ahead of the scheduled PFS/FV application visit.

A 3 digit participant ID for each child will be assigned sequentially as each child is entered on the Screening & Enrolment log by the CDS for each school. This will be prefixed by a 2 digit school ID to form a unique identifier for each child which will be used for the purpose of participant identification and data collection during the trial.

As this study is blinded only from the perspective of the assessor (i.e. dentist performing ICDAS caries assessment), the randomisation list will be readily available to the remaining members of the study should the need arise to identify what intervention a particular child has received in order to respond to a specific clinical situation.

5.9. Screening and enrolment logs

A screening and enrolment log will be prepared for each school and will be populated from the Year 2/3 class lists provided by the school. The log will record dates when informed consent and medical history forms have been distributed and if and when they are returned, whether a child has been enrolled onto the study and any reasons for a child being excluded. This information will be recorded so that any biases from differential recruitment will be detected. The screening and enrolment log will be maintained by the MDC and a copy will be sent to the Seal or Varnish Trial Manager at regular intervals to allow close monitoring of recruitment progression.

6. TRIAL INTERVENTIONS

As discussed in Section 3.1, the two technologies evaluated in this trial (PFS and FV) are well established and have been used routinely to prevent dental caries for several decades. Eligible participants will be randomised to receive either PFS or FV, and will remain on the intervention to which they have been randomised for the duration of the study.

6.1. Pit and Fissure Sealant (PFS)

The PFS used for evaluation in the study is Delton® Light Curing Opaque Pit & Fissure Sealant (Dentsply Ltd; CE0086), which is the same PFS used in the current school based Designed to Smile programme described above. PFS will be supplied as 2.7 ml bottles for multiple applications and applied topically as a thin layer to occlusal surface of eligible teeth.

Initial application of PFS will occur within 2 weeks of the baseline dental examination, and will be performed by a suitably qualified and trained dental hygienist according to the conventional clinical protocol established by the CDS (Appendix 1).

The condition of the PFS will be re-examined at 6, 12, 18, 24, and 30 months, and will be re-applied if the existing sealant has become detached, or if attachment is considered insufficient.

All applications of PFS will be documented on a treatment record form, which will capture the date, batch number, patient ID number and number of applications (i.e. teeth) performed.

6.2. Fluoride Varnish (FV)

The FV used for evaluation in the study is Duraphat® 50 mg/ml dental suspension (Colgate-Palmolive (UK) Ltd; PL 00049/0042), equivalent to 22,600ppm fluoride. FV will be supplied as 10 ml tubes for multiple applications and applied topically as a thin layer to the pits, fissures and smooth surfaces of eligible teeth. As per the Duraphat® Summary of Product Characteristics (SmPC), dosage per single application will not exceed 0.4 ml.

Initial application of FV will occur within 2 weeks of the baseline dental examination, and will be performed by a suitably qualified and trained dental hygienist according to the conventional clinical protocol established by the CDS (Appendix 2). FV will be re-applied at 6, 12, 18, 24, and 30 months.

All applications of FV will be documented on a treatment record form, which will capture the date, batch number, patient ID number and number of applications (i.e. teeth) performed.

6.3. Supply, packaging and reconciliation of trial materials

Acquisition, labelling, distribution and reconciliation of both PFS and FV will be performed by St. Mary's Pharmaceutical Unit (SMPU), which is a pharmaceutical manufacturing facility and part of the Cardiff and Vale University Health Board.

The primary packaging of PFS and FV will be labelled to identify the product, and will state 'for clinical trial use only'. Also included on the label will be the name of

the Co-chief Investigators, the expiry date of the product, the batch number (relating to assembly) and a unique identifier for that tube/bottle.

As the technologies to be evaluated in this trial are marketed products to be administered/applied to the intended patient population according to the indication specified by the marketing authorisation (by a dental hygienist in an established Cardiff and Vale UHB mobile dental clinic), both PFS and FV will be supplied in containers intended for multiple applications and therefore the label will not be specific to a particular patient.

This approach has been discussed with the MHRA (via the MHRA clinical trials helpline) and is currently employed in a related clinical trial performed in a primary dental care setting investigating FV as part of a caries prevention regime (Northern Ireland Caries Prevention in Practice Trial; EudraCT 2009-010725-39).

Trial materials will be stored under the conditions specified by the manufacturer (or SmPC in the case of Duraphat®) by SMPU. They will be distributed from SMPU to the MDC as required (in primary packaging only), following a request from the MDC team to the trial manager. Upon receipt by the MDC team, all clinical materials will be stored separately to non-trial materials in a locked cabinet at the CDS offices until required for administration on the MDC. The exact processes for the management of trial materials will be described in a Standard Operating Procedure specific to this trial, developed in conjunction with and approved by a Cardiff & Vale UHB clinical trials pharmacist.

After use, all trial materials will be retained by the MDC team for collection by the trial manager for subsequent return to SMPU.

6.4. Dose modification for toxicity

The total dose of FV will depend on the number of eligible teeth to be treated, and will not exceed 0.4 ml per single application (as per Duraphat® SmPC).

The PFS does not have an associated maximum dose, as this product does not contain an active pharmaceutical ingredient.

In the event of a suspected adverse drug reaction (including an allergic reaction) to either product, the patient will be withdrawn from trial treatment (See Section 7.5 for Withdrawal Procedures and Section 8 for Pharmacovigilance aspects of the trial).

6.5. Interaction with other drugs

Parents of children participating in the study will be advised to avoid giving their children fluoride-containing dental medication (tablets, gels etc) other than their normal fluoride toothpaste (if used) for the duration of the trial.

7. TRIAL PROCEDURES

7.1. Training of staff

The MDC team involved in the clinical aspects of this trial will be selected by the CDS, from the existing Designed to Smile programme. As such they will already be trained in the majority of the trial procedures, including application of both PFS and FV according to the conventional clinical protocols established by the CDS.

All staff involved in the trial specific procedures (including recruitment/consent, collection of trial data, application of interventions and clinical assessments) will be trained in GCP.

Prior to the start of recruitment the trial management team will provide trial-specific training to the MDC team, including practical/logistical aspects and appropriate collection of trial data using the CRFs.

Dentists involved in the ICDAS caries assessment will undergo a training and calibration exercise prior to the baseline dental examination. This will involve assessment of caries using ICDAS in up to thirty five, 6-7 year old primary school children from Community First schools in South Wales. The protocol for the training and calibration exercise is presented in Appendix 7.

7.2. Data collection/assessment

The schedule for timing, frequency and method of collection of all trial data is summarised in Tables 1 and 2. Assessments will be performed as close as possible to the required time point. Where an assessment cannot be performed within a reasonable timeframe around the required timepoint this will be documented in the patients case report form (CRF), including the reason for missing the assessment (e.g. child absent from school).

Training for completion of trial CRFs will be provided to the applicable CDS staff members prior to the trial commencing. CRFs should be completed in black ball point pen, with unique participant ID number, initials and date of birth recorded on the header of each individual form. Incorrectly entered information should only be amended on the original CRF prior to photocopying. Corrections should be made by deleting with a single line through the entry and writing the correct value alongside the box; all amendments should be initialled and dated. Once complete, the CRFs will be photocopied and the originals should either be sent via recorded delivery to SEWTU on a weekly basis, unless collection by a member of the trial management team at SEWTU/delivery by a member of the CDS team has been agreed in advance. The photocopy of the CRF should be filed in the appropriate School CRF folder at the CDS offices.

7.3. Informed Consent Procedure.

The procedure for recruitment and obtaining informed consent is described in Sections 5.5 and 5.6

7.4. Randomisation procedure

The procedure for randomisation is described in Section 5.8.

7.5. Withdrawal Procedure

Children may be withdrawn from trial treatment or the trial by the parent for any reason, at any time, without their future dental care being affected. Where this situation arises the parent will be contacted to determine the reason for withdrawing their child to allow the Trial Management team to complete a Trial Withdrawal form.

The Investigator may withdraw a child from the trial treatment at any time if he/she considers that the child's health or wellbeing is compromised by remaining in the trial. Any withdrawals by the Investigator will be documented via completion of the Trial Withdrawal form. The child's parent will be notified of the child's withdrawal by telephone.

The MDC team will notify SEWTU of the withdrawal by telephone as soon as possible, and arrangements made for the withdrawal form to be sent via fax (if possible). The trial manager will liaise with the MDC team to obtain the hard copy of the form at the next available opportunity.

7.5.1. Withdrawal from Trial Treatment

Specific reasons from discontinuing children from trial treatment are:

- Voluntary discontinuation by the child's parent (see above)
- Safety reasons as judged by the Investigators and/ or sponsor (i.e. allergic reactions)
- Incorrect enrolment (i.e. the participant does not meet the required inclusion/exclusion criteria)

7.5.2. Withdrawal from trial

If the parent explicitly withdraws consent to have their or their child's data recorded, their decision must be respected and recorded on the withdrawal form. Details of the withdrawal from should be noted in the participant's records and no further CRFs should be completed on the child.

Table 1 – Assessment schedule

Data Type	Prior to Baseline Evaluation	Baseline Evaluation	Randomisation & Initial PFS/ FV Application	Follow Up Period (months)					
				6	12	18	24	30	36
Clinical Data									
Medical/Dental History/Demographics	X				X		X		
Eligibility (Inclusion/Exclusion Criteria)		X	X						
Caries Risk Related Habits			X		X		X		X
ICDAS caries assessment		X			X		X		X
Pre-treatment assessment[1]			X	X	X	X	X	X	
Adverse Event assessment			X	X	X	X	X	X	X
Health Economics Data									
NHS resource usage interviews			X		X		X		X
Parental Resource Questionnaire			X		X		X		X
School Resource Questionnaire			X		X		X		X
Health-related Quality of Life (CHU9D)					X		X		X
Treatment Acceptability & Process Evaluation Data									
Observational Scale [2]			X	X	X	X	X	X	
Delighted-Terrible Faces Scale			X	X	X	X	X	X	
Interviews with children			X						X
Interviews with parents			X						X
Questionnaires/Interviews with schools[3]			X						X
Interviews with Dental Team[4]			X		X		X		X
Interviews with non-consenting parents	I< ---------- >I								
Interviews with non-responding parent	I< ---------- >I								
Interviews with withdrawing parents			I< ---------- as required ---------- >I						

[1] Assessment limited to condition of previously-applied sealant and/or pre-application risk assessment for sealant/varnish
[2] Completed by both Dental Hygienist **and** Dental Nurse during/immediately after treatment
[3] All schools will be asked to complete a questionnaire at the beginning of the study with a sample of schools invited for telephone interview at the end of the study
[4] Dental Team composed of Dental Officer, Dental Hygienist and Dental Nurse

Table 2 – Data Collection Summary

Data Type	Subject of assessment	Person(s) performing assessment/collecting data	Method of assessment
Clinical Data			
Medical/Dental History/Demographics	Child	Parent	Medical History Form completed by parents (Section 7.6.3)
Eligibility (Inclusion/Exclusion Criteria)	Child	Parent/Dental Team[3]	Determined from Medical History Form or Baseline clinical examination (Section 5.4)
Caries Risk Related Habits[1]	Child	Parent	Postal Questionnaire (See Section 7.6.3)
ICDAS caries assessment	Child	Dental Officer	Clinical examination in MDC (See Section 7.6.2)
Pre-treatment assessment[2]	Child	Dental Hygienist	Clinical examination in MDC (as per Appendices 1 & 2)
Adverse Event assessment	Child	Dental Team	Recorded as reported by child/parent (Section 8).
Health Economics Data			
NHS resource usage interviews	CDS staff	Member of trial team	Structured Interview (Section 7.7)
Parental Resource Questionnaire	Child & Parent	Parent	Postal Questionnaire (Section 7.7)
School Resource Questionnaire	Headteacher[4]	Member of trial team	Structured Questionnaire (See Section 7.7)
Health-related Quality of Life (CHU9D)	Child	Child	Postal questionnaire[5] (See Section 7.7)
Treatment Acceptability & Process Evaluation Data			
Observational Scale[6]	Child	Dental Hygienist/Dental Nurse	Dental Hygienist/Dental Nurse (Appendix 6)
Delighted-Terrible Faces Scale	Child	Child	Child-completed questionnaire[5] (Appendix 5)
Interviews with children	Child	Member of trial team	Face-to-face Interview (See Section 7.8.2)
Interviews with parents	Parents	Member of trial team	Telephone Interview (See Section 7.8.3)
Questionnaires/Interviews with schools	Headteacher[4]	Member of trial team	Questionnaire/Telephone Interview (See Section 7.8.4)
Interviews with Dental Team[3]	Dental Team	Member of trial team	Face-to-face Interview (See Section 7.8.5)
Interviews with non-consenting parents	Non-consenting parents	Member of trial team	Telephone Interview (See Section 7.8.6)
Interviews with non-responding parents	Non-responding parents	Member of trial team	Face-to-face Interview (See Section 7.8.6)
Interviews with withdrawing parents	Withdrawing parents	Member of trial team	Telephone Interview (See Section 7.8.6)

[1] Questionnaires for Caries Risk-Related Habits and Parent Resources combined to form one postal questionnaire for parents to complete (Appendix 3)
[2] Assessment limited to condition of previously-applied sealant and/or pre-application risk assessment for sealant/varnish
[3] Dental Team composed of Dental Officer, Dental Hygienist and Dental Nurse
[4] or staff member with greatest involvement in trial at school
[5] Delighted-Terrible Faces Scale Completed within 2 hours of receiving treatment; CHU-9D completed by child at home under supervision of parent.
[6] Completed by both Dental Hygienist **and** Dental Nurse during/immediately after treatment

7.6. Clinical Assessments

7.6.1. Patient Eligibility

The demographic and medical history information collected from the parents will be reviewed to determine if the child meets inclusion/exclusion criteria prior to a clinical examination. Children considered eligible following this stage will undergo a baseline clinical examination to determine eligibility based on the clinical inclusion/exclusion criteria (detailed in Section 5.4).

7.6.2. ICDAS caries assessment

Caries status will be assessed at baseline for all children considered eligible. Caries status will be assessed and recorded by trained and calibrated dentists using conventional diagnostic caries criteria at the d_1/D_1- d_3/D_3 level in accordance with nationally recognised diagnostic criteria (Pitts, 2004). Data will be recorded using charts specifically designed for collection of ICDAS dental codes (www.icdas.org).

In addition to baseline, a clinical examination including ICDAS caries assessment will be performed at 12 month intervals for 36 months.

As part of the annual caries assessment approximately 5% of study participants will be re-examined to determine intra-examiner reproducibility. Full details of this analysis will be described in the Statistical Analysis Plan.

7.6.3. Medical History and Caries Risk Related Habits

The medical history of the child will be ascertained by asking the parents to complete a medical history form, which will collect data specifically relating to: allergies; asthma (including whether this has resulted in hospitalisation); sensitivity to constituents of either PFS or FV; if the child is currently participating in a clinical trial involving an IMP. Whether or not the child is registered with a GDP will also be ascertained.

Following enrolment onto the trial, any changes to the child's relevant medical history (as described above) will be ascertained by enclosing a brief Medical History Follow-Up Form with the postal questionnaires (detailed below and in Section 7.7) sent to parents on an annual basis during the trial. Parents will be instructed to complete and return the Medical History Follow-Up Form to the dental team only if there has been a change in relevant medical history.

For children deemed eligible to participate in the trial, information relating to the caries risk related habits will be obtained via a postal questionnaire (Appendix 3) sent to parents at baseline, 12, 24 and 36 months post treatment.

7.6.4. Adverse Event assessment

During the course of the study, the occurrence of any serious adverse events (SAEs)/serious adverse reactions (SARs) (detailed in Section 8.1) will be ascertained and recorded using the study SAE form.

Parents will be asked to report to the CDS team any dental/medical problems experienced by their child for a 48 hour period following each treatment.

The procedure for reporting SAEs/SARs is described in Section 8.4.

7.7. Health Economics Assessment

The economic analysis will estimate the costs of providing the PFS versus FV, and the consequences of the scheme for the NHS, children and their families, education and society.

In principle the following analyses will be undertaken:

- Costs for each trial participant will be calculated. Number and frequency of service utilisation will be multiplied by the relevant unit cost (derived from published sources: Curtis, 2009; NHS Reference Costs 2009) to produce a total cost per participant.
- Travel costs and other costs to families associated with provision of PFS and FV will be collected using structured questions.
- Assessment of the total cost of PFS and FV including potential costs of treatments avoided.

The identification and collection of costs will be undertaken using the following methods.

1) NHS.

Data on the use of community health dental resources will be collected through structured interviews with key relevant dental and finance staff and main trial team. A micro-costing exercise will also be undertaken to assess direct costs to the NHS. This will include staff resources (e.g. number, grades of staff), treatment/appointment duration; equipment and materials used. These will be logged on resource utilisation recording sheets at each clinic and costed using published unit costs (Curtis, 2009; NHS Reference Costs 2009) and list prices e.g. British National Formulary.

2) Children and families

The costs to families (including the child) will be collected using a Parental Resource Utilisation (PRU) questionnaire, which will be combined with questions relating to Caries Risk Related Habits (Section 7.6.3) to form a single postal 'Dental Health' questionnaire to be completed by parents (Appendix 3). This brief questionnaire will capture information on any time away from work/other paid activities to attend the child's appointment or other dental appointments; any medication for dental-related problems and normal dental hygiene practice at home for the child. In addition, parental occupation will be captured. As with Caries Risk Related Habits, this information will be collected at baseline, 12, 24 and 36 months post treatment.

The health-related quality of life (HRQoL) of children will be measured using the CHU-9D questionnaire (Stevens 2009, Stevens 2010a; Appendix 4). The CHU-9D questionnaire will be sent to parents with instructions to ask the child to complete it, providing assistance if required. CHU-9D questionnaires will be sent out at

12, 24 and 36 months following the initial treatment. Utility values will be calculated to derive quality adjusted life years (QALYs).

3) Education

Data on the use of school resources will be collected through the administration of a structured questionnaire with the headmaster from participating schools. This will include time of the child away from classroom/usual school activities, school administration time, teacher time, other school personnel time and other school resources utilised. This information will be collected alongside the collection of information via the headmaster questionnaire survey on the acceptability, feasibility and sustainability of the programme in Schools.

4) Implementation costs

Costs of implementing the interventions are not applicable to this study as the MDC is already established. However, the analysis will take into account the depreciation costs of the clinic over the trial period and beyond as part of the sensitivity analysis.

5) Research costs

These will be separated from the other costs incurred to provide clarity. The research costs incurred as a result of establishing the study, training, running the evaluation, completing questionnaires will be collected through discussion with the main trial team.

7.8. Treatment Acceptability Assessment and Process Evaluation

Treatment acceptability will be assessed in three ways, acceptability scales will be completed by clinical staff and all children participating in the trial (Section 7.8.1). In addition qualitative interviews will be conducted with a subsample of children (Section 7.8.2).

Summaries of the various approaches planned for treatment acceptability and process evaluation are described in Sections 7.8.1 to 7.8.6. Full details of the planned assessment/evaluation, including interview schedules and the methods for contacting non-participants are described in a separate **Process Evaluation Plan**.

7.8.1. Treatment Acceptability Scales

The observation scale (Appendix 6) will be provided for dental hygienists and dental nurses to complete for each child during treatment application of PFS or FV.

Treatment acceptability will also be assessed from the child's perspective through a Delighted-Terrible Faces (D-T) scale (Appendix 5), completed by all children in the MDC immediately following the initial application of PFS/FV, and at each follow up visit.

7.8.2. Interviews with Children

A sample of schools participating in the trial will be selected for the purpose of conducting acceptability interviews with children. Lists of children (identified by unique ID number, initial and date of birth) participating in treatment for each school will be produced, and will be divided into trial arm. Children will be purposively sampled from each trial arm group for a range of acceptability scores to ensure a spread of maximum difference across the sample. In total 48 children (24 from each trial arm) will be interviewed. The staff member(s) responsible for trial aspects at each school will assist in inviting the sampled children to attend an interview in pairs . Face-to-face, paired interviews will be conducted with children in a school setting up to two weeks after their first and last treatment to ensure children will have a reasonably accurate recall of their experience of treatment. Interviewers will be provided with information about the initial D-T scale and observation scale results for each interviewee prior to the interviews to inform how questions are asked. The scale results will not be discussed during interviews, however, to ensure confidentiality.

7.8.3. Interviews with Parents

Parents of sampled children will be interviewed, with 24 parents interviewed in each trial arm and, once sampling has taken place, will be notified that a researcher will be telephoning them for an interview. Parents will be interviewed by telephone four to six weeks after their child's first and last treatments. Interviewers will be provided with information about D-T scale and observation scale results for each interviewee's child to inform how questions are asked but will not be discussed, to ensure confidentiality.

7.8.4. Questionnaires/Interviews with Schools

All schools will be asked to complete a questionnaire at the beginning of the study regarding their experience with implementation of the trial. At the end of the study a number of schools will be purposively sampled based on responses to the questionnaires and the member of staff within each participating school who has the most involvement in the trial will be invited to take part in a telephone interview to investigate the impact of the trial on the school and the implications of this for the acceptability and feasibility of the trial in a community setting.

7.8.5. Interviews with the Dental Team

The dental team delivering the treatment will be interviewed annually in order to assess how the trial is implemented, factors which promote or impede implementation, perceptions of patient acceptability, and experiences of working with schools.

7.8.6. Interviews with Non-Participants

Up to 20 withdrawing parents will be contacted for an interview and will be compared by trial arm. A sample of up to 20 non-responding and up to 20 non-consenting parents will also be contacted for interview. The process for making contact with non-consenting/non-responding parents is described in detail in the study Process Evaluation Plan.

7.9. Follow-up

Children will be followed up at six monthly intervals for 36 months following initial application of PFS/FV. Clinical, treatment acceptability and health economic assessments will be performed according to Table 1, and as detailed in Sections 7.6 to 7.7.

There is potential for children to have moved away from the area, discontinued their treatment or be absent from school at the final examination. These anticipated losses to follow up have been accounted for in the sample size calculation.

In order to maximise the collection of the data obtained via the postal Dental Health and CHU-9D questionnaires, parents will be contacted by telephone where questionnaires have not been returned within approximately 2 weeks of being sent. If requested by the parent, one additional questionnaire (for each questionnaire type) will be sent out for each timepoint during the study.

7.10. Treatment/Assessment Windows

Visits to schools by the MDC will be coordinated to allow treatments and assessments to be performed as closely to the planned intervals presented in Table 1 as possible. However, it is recognised that due to the nature of the setting and potential for disruption (due to weather and other unforeseen circumstances), a window of ±1 month for all treatment and assessment visits will be observed, with the exception of the interval between baseline dental examination and initial treatment which will be between 2 and 8 weeks.

Similarly to clinical assessments and treatments, a window of ±1 month for all interviews and questionnaires for the collection of health economics, treatment acceptability and process evaluation data will be observed.

Interviews with non-consenting and non-responding parents are planned to be conducted between the start of recruitment and initial treatment, but are not subject to a fixed assessment window. Withdrawing parents will be contacted for interview within one month of withdrawal wherever possible.

8. PHARMACOVIGILANCE

8.1. Definitions

The following definitions are in accordance with both the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and the subsequent amendment regulations (SI2006/1938) and ICH-GCP:

Adverse Event (AE): Any untoward medical occurrence in a clinical trial participant to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

Adverse Reaction (AR): Any noxious and unintended response in a clinical trial participant to whom an IMP has been administered, which is related to any dose administered. A "response" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* Note: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Adverse Reactions (SARs): Any Serious Adverse Event occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSAR): These are **SARs** which are classified as 'unexpected' i.e. an adverse reaction, the nature and severity of which is not consistent with the applicable information about the medicinal product outlined in the SmPC for Duraphat®, or in the information provided by the manufacturer for Delton®.

Expected adverse reactions with trial treatments are tabulated below:

Delton® – Light Curing Pit and Fissure Sealant	Anaphylactic reactions in susceptible individuals Inflammatory changes of the oral mucosa
Duraphat® 50 mg/ml Dental Suspension	Gastrointestinal disorders: Gingivitis ulcerative, Nausea, Odema mouth, Retching, Stomatitis in sensitive (allergic) individuals Skin and subcutaneous tissue disorders: Angioedema, Irritation in sensitive individuals Respiratory, thoracic and mediastinal disorders: Asthma

Please note: Although the information provided in the above table was comprehensive at the time the current protocol version was produced, the list of side effects may have been subsequently updated and the site/Investigator should refer to EMC Medicines for updated information.

8.2. Causality

Most adverse events and drug reactions that occur in this trial, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this trial. The assignment of the causality should be made by the Investigator responsible for the care of the participant using the definitions in the table below.

The Chief Investigator (or Clinical Reviewer Delegate) will also be responsible for making an assessment of causality.

In the case of discrepant views on causality between the site and the clinical reviewer, the event will be handled at the highest event categorisation.

Causality of every SAE should be assessed using clinical judgement based on the information available to determine the relationship between the SAE and the intervention received by the participant. For the purpose of this trial, relationships will be classified as one of the following: not related; unlikely to be related; possible related; probably related; definitely related.

Relationship	Description
Unrelated	No evidence of any causal relationship with the trial/intervention
Unlikely	Little evidence to suggest there is a casual relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	Some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	Evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	Clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

8.3. Events exempt from SAE reporting:

The following events are exempt from reporting as SAEs in the Seal or Varnish trial:

- Any adverse event or reaction occurring more than 48 hours after treatment will not be reported.
- Non-serious adverse events/adverse reactions will not be recorded as part of the study, and will be managed according to current clinical practice
- Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures for a pre-existing condition.

Information relating to these events will be captured on the relevant CRF instead.

8.4. Reporting Procedures

As per the current Designed to Smile Fissure Sealant programme, clinical staff involved in delivery of the intervention will monitor participants during and immediately following administration of sealant/varnish and manage any adverse events/reactions according to current clinical practice.

Parents will be asked (via a Treatment Follow-Up Letter taken home with the child, as per current practice) to notify the dental team of any significant medical/dental issues that occur within 48 hours of the child receiving treatment in order to identify any SARs or SAEs that occur outside of the MDC.

Any queries concerning adverse event reporting should be directed to the trial coordination centre in the first instance. A flowchart is given below to illustrate reporting procedures.

8.4.1 Site Responsibilities

SAEs will be reported from the time a participant is randomised onto the trial until 48 hours after the participant receives their last application of PFS/FV.

All SAE forms should be reported to the SoV TM at SEWTU within 24 hours of the local site becoming aware of the event via completion of an SAE form.

The responsible Investigator should sign the causality of the event. **No assessment of expectedness will be provided by the Investigator responsible for the care of the participant.**

The assessment of whether or not an Adverse Reaction is an expected reaction from the administration of the IMP will be provided by the Chief Investigator (or Clinical Reviewer Delegate). This assessment will be based on the approved Reference Safety Information for the IMP.

Completed forms should be signed and dated and sent (preferably by fax) to the SoV Team at SEWTU together with relevant treatment forms and anonymised copies of all relevant investigations.

Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting. All events should be followed up through to resolution.

SAEs will be followed up by the dental team until they are resolved or the Investigator assesses them as chronic or stable. The follow up and outcome of SAEs will be documented in the appropriate case report form.

Additionally, SEWTU/pharmaceutical companies may request further information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

8.4.2 Sponsor Responsibilities

The responsibility of pharmacovigilance has been delegated by the Sponsor to SEWTU and therefore all reported SAEs will be followed up by the trial team until they are resolved or the Investigator assesses them as chronic or stable.

SEWTU will notify the MHRA, main REC and Sponsor of all SUSARs occurring during the trial according to the following timelines, where day zero is defined as the date the SAE form is initially received at SEWTU:

- SUSARs which are fatal or life-threatening must be reported not later than 7 calendar days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 calendar days.
- SUSARs that are not fatal or life-threatening must be reported within 15 calendar days of the sponsor first becoming aware of the reaction.

A list of all SARs/SAEs (expected and unexpected) will be reported annually to the MHRA and REC by SEWTU in the Development Safety Update Report.

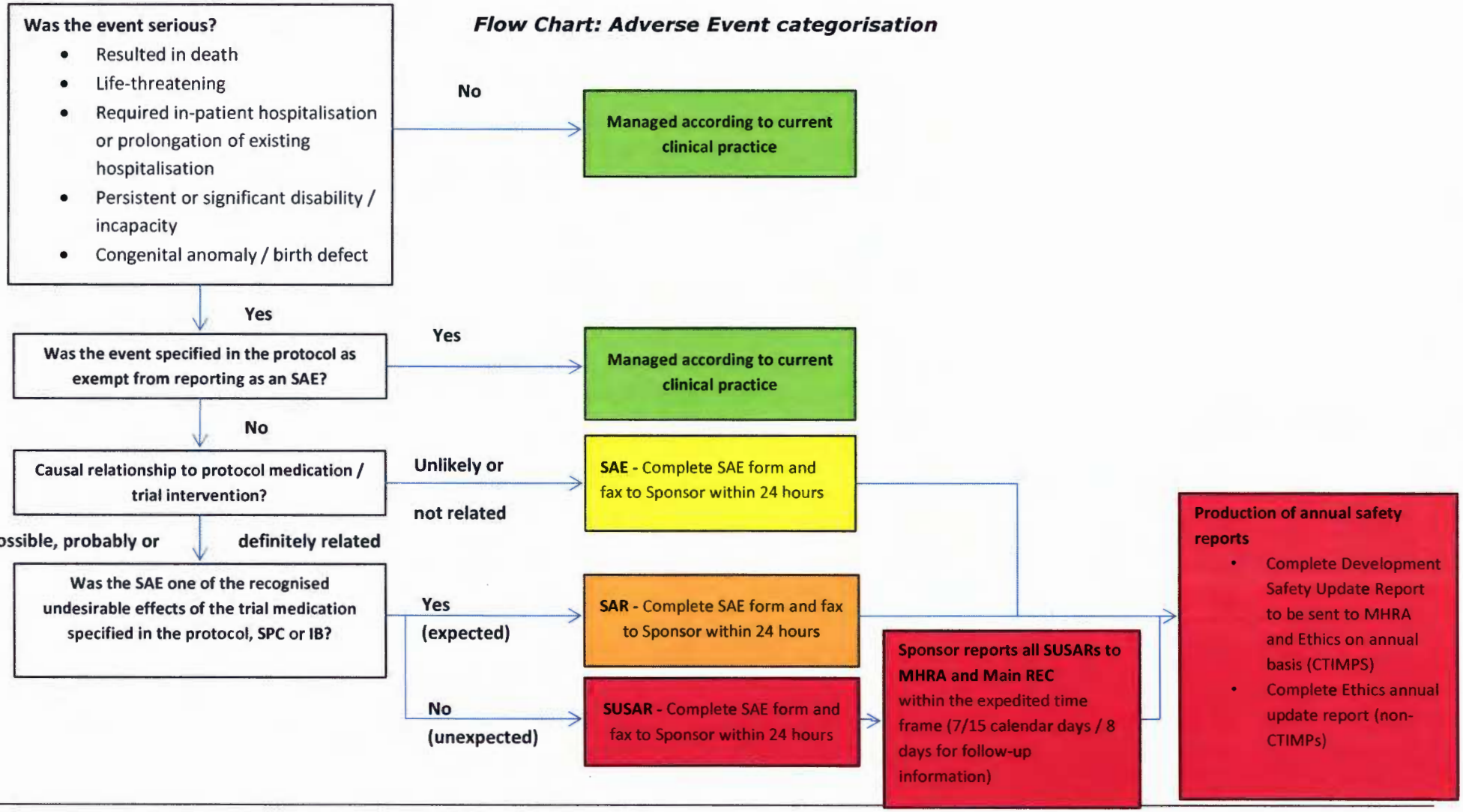
Contact details for reporting SAEs, SARs and SUSARs

Please Fax to:

02920 687612, attention: C. Lisles

Queries:

Tel: 02920 687921 (Mon to Fri 09.00 – 17.00)


Flow Chart: Adverse Event categorisation
Was the event serious?
Resulted in death
Life-threatening
Required in-patient hospitalisation or prolongation of existing hospitalisation
Persistent or significant disability / incapacity
Congenital anomaly / birth defect
No
Managed according to current clinical practice
Yes
Was the event specified in the protocol as exempt from reporting as an SAE?
Yes
Managed according to current clinical practice
No
Causal relationship to protocol medication / trial intervention?
Unlikely or not related
SAE - Complete SAE form and fax to Sponsor within 24 hours
possible, probably or definitely related
Was the SAE one of the recognised undesirable effects of the trial medication specified in the protocol, SPC or IB?
Yes (expected)
SAR - Complete SAE form and fax to Sponsor within 24 hours
No (unexpected)
SUSAR - Complete SAE form and fax to Sponsor within 24 hours
Sponsor reports all SUSARs to MHRA and Main REC within the expedited time frame (7/15 calendar days / 8 days for follow-up information)
Production of annual safety reports
Complete Development Safety Update Report to be sent to MHRA and Ethics on annual basis (CTIMPS)
Complete Ethics annual update report (non-CTIMPs)

9. STATISTICAL CONSIDERATIONS & ANALYSIS

9.1. Trial outcomes

9.1.1. Primary outcome measures

(i) Dental caries outcome measures

The primary outcome measure will be the development of dental caries on first permanent molars at 36 months (Pitts 2004).

(ii) Outcomes measures for Health Economic Analysis

In terms of outcomes, the indicators of effect for clinical effectiveness will be used alongside costs to estimate the relative cost-effectiveness of the PFS and FV. As part of the analysis we will stratify by baseline dental caries status in order to undertake sub-group analysis.

Two additional outcome measures will be used for cost-utility analysis (CUA). These will be used to estimate Incremental costs per QALY estimates.

a) Health –related quality of Life (HRQOL)

The CHU9D is a generic preference based measure of HRQOL for use in children. This questionnaire has been developed by the School of Health and Related Research (SHARR), based at Sheffield University. It has been developed exclusively with primary school-aged children. This included interviews with over 70 children with a wide range of health problems, with further ranking work to develop a draft questionnaire. This was tested on 150 school children and 98 children in hospital to produce the final questionnaire (Stevens, 2009; Stevens, 2010a). Preference weights for the CHU-9D were obtained from a sample of the UK general population (Stevens, 2010b).

The CHU9D consists of a set of 9 questions (dimensions) with 5 levels of responses available per question. It has a recall period of today/last night and is intended to be self-completed by the child. It has been developed for use in children aged 7-11 years, with an average time of 3.4 minutes to complete and it has been confirmed by the developers that it should be suitable for the expected age range within this trial (Stevens, 2009b). However, as some of the children will be younger than those for which the CHU9D has been validated (i.e. 6-7 years at initial study entry) prior to the start of recruitment for this clinical trial, a pilot study will be conducted in a primary school in South Wales to ensure the CHU9D can be appropriately implemented during the early stages of this trial.

b) Quality Adjusted Tooth Years (QATYs)

Utility values will be measured as QATYs (Birch, 1986; Bhuridej et al., 2007) which is the production of additional years of life (tooth-year) of each tooth adjusted for the quality of the tooth. An unrestored tooth has a QATY equal to 1 in the year it was restoration –free, whilst a restored, crowned, or root canal treated tooth has a QATY of less than perfect (i.e. less than 1) in the year that it was restored and subsequent years. The QATY for an extracted tooth is equal to 0

in that year and subsequent years. Data to inform the calculation of QATYs will be derived from the clinical data collected

9.1.2. Secondary outcome measures

A modified version of the Delighted-Terrible Faces Scale (Andrews and Withey, 1976, Marshman and Hall, 2008) will be used with children to determine patient acceptability. During the clinical placement of the technologies under investigation, dental hygienists and dental nurses will record the following indicators of patient acceptability/adverse outcomes: vomiting, crying, gagging, excessive arm/leg movements and other signs of distress (Hawkins et al, 2004). These data will be triangulated with each other and via a series of semi-structured interviews with children, parents, school staff and clinical personnel on treatment acceptability.

The process evaluation will explore how parents, children, schools and clinicians experienced the implementation of the treatment programme, factors which effected how treatment was delivered, and how individuals involved responded to the programme. This aspect of the study will assess how this type and design of programme is implemented in a community setting and what factors facilitate or hinder implementation and successful treatment.

Interviews with parents who withdraw from the trial, did not consent or did not respond will be conducted to explore factors affecting participation in the trial. This will enable the study to explore reasons for non-participation or withdrawal, and any potential for study bias due to characteristics of parents and children who do not participate.

9.2. Randomisation

Randomisation will be stratified by school and balanced on a number of clinically important stratification factors using minimisation in a 1:1 ratio for treatments. An additional random component will be added to the minimisation algorithm (Altman 2005) such that it is not completely deterministic.

9.3. Sample size

Data from a cohort study among primary school children under the care of the Cardiff and Vale University Health Board CDS was used to derive the caries incidence in children (mean age 6.5yrs) with at least one erupted first permanent molar (Treasure et al. 2005). 40% had caries in one or more of their first permanent molars by the age of 10. Based on recent Cochrane reviews it is estimated that FV would reduce the 3 year incidence from 40% to 30% in this population (Marhinho et al. 2002), whereas PFS would reduce it further to 20% (Ahovuo-Saloranta et al 2008). For an individually randomised trial at a power of 80% with a significance level of 5%, at least 313 children per group are required for a comparison of 20% vs 30% at 3 year follow-up.

The following assumptions have been made to ensure the necessary recruitment and retention: 2,820 parents will be invited to consent to their child's participation in the trial, associated with an estimated 40% (n=1,128) refusal rate. This is inflated from the current 10% of parents who refuse participation in

the existing Designed to Smile programme. Experience from the existing programme shows that 2% (n=34) of consented children will refuse to cooperate to allow PFS placement and an estimated 1% (n=16) will be excluded on medical grounds. Again based on the current programme, an anticipated 44% (n=722) of consented children will lack an erupted FPM and therefore be ineligible for randomisation.

The above attrition is estimated to leave 920 participants to be randomised to the technologies being evaluated (460 per arm). An 8% (n=204) per annum loss to follow-up has been assumed based on the current programme and a previous cohort study (Treasure et al. 2005). Finally a 5% absence at the final examination has been assumed, leaving 680 children for analysis at the final examination.

9.4. Interim Analysis

The Independent Data Monitoring Committee (IDMC) will be presented with clinical (including adverse event) and recruitment data at least annually in order to determine if the study proceeding is justified.

9.5. Final Analysis

9.5.1. Primary Outcome analysis

(i) Analysis of dental caries

The primary analysis will be an Intention to Treat Analysis (ITT) and comprise a comparison of the proportion of children developing caries in at least one of their permanent molars at 36 months follow-up, as randomised between the two arms of the trial. Logistic regression will be used to model caries outcomes with age, gender and baseline caries as covariates. Multi-level modelling will be used to account for clustering at school level. Child and school level characteristics will also be collected, such as use of fluoride toothpaste and oral hygiene routine, size of school, postcode and participation in the oral health education programme (Appendix 3). Secondary analyses will involve multilevel logistic regression modelling of the tooth level data. Child, tooth and surface level caries data as well as sealant retention and oral hygiene will be included in the model. A per protocol analysis will also be carried out to estimate treatment efficacy in those children with complete treatment compliance. A sensitivity analysis will be performed to estimate any selection bias introduced by the per-protocol analysis in comparison to the ITT analysis and the effects of loss to follow-up under the assumption that those lost have poorer caries outcome.

(ii) Analysis of Health Economics

The economic analysis will mirror the approaches employed in the analysis of clinical data. Full details regarding the analysis of Health Economics will be documented in a separate Health Economics Analysis Plan.

Budget Impact Analysis

The budget impact analysis will be undertaken for the 1 year and 3 year periods and will compare the costs to the NHS of providing the preventative measures with the potential resources released as a result of reduction in dental caries.

9.5.2. Secondary Outcome Analysis

The aims of the analysis of secondary outcomes and process evaluation are to assess:

- Treatment acceptability from children and parents' perspectives, and comparison of acceptability between PFS and FV
- Issues affecting the implementation of the trial in a community setting from the perspectives of children, parents, schools and clinicians, including longitudinal aspects
- To identify potential bias through investigating non-participants and those who do not consent or withdraw from the trial

Interviews will be tape recorded and transcribed, and will then be analysed using framework analysis (Ritchie et al. 2003). Framework analysis is a method which organises responses by respondent and interview content, and will facilitate data triangulation as categories of responses by different groups can be compared more easily.

Treatment Acceptability

The Delighted-Terrible faces scale will be the primary instrument used to measure patient acceptability since this will produce data with less bias than the observation scale (Hawkins et al., 2004) completed by the dental hygienists and dental nurses. Data will be triangulated between child and parent interviews, the D-T scale and acceptability ratings to investigate data validity, and also to explore reasons for high and low acceptability ratings. Data will also be compared by trial arm in order to compare PFS and FV acceptability and reasons for any differences, and will also be analysed for change over time.

Implementation of Trial (Process Evaluation)

Interview data will be analysed to determine factors assisting or hindering the implementation of the trial in a community setting. Interview data will analysed for each group to assess perspectives of each group (schools, clinicians, children and parents) and will be triangulated between groups to ensure data validity. Interview data will also be analysed to assess whether trial experience of children, parents and schools changed over time.

Potential Bias

Interview data from parents who did not respond, not consent or who withdrew from the trial will be analysed to assess reasons for non-participation, including perceptions of the treatment, research involvement and contextual factors in the lives of parents and children which affect participation. Data on treatment acceptability will also be analysed for children who withdrew from the trial. This

analysis will also include an assessment of any potential bias in the trial. Interviews with children will be analysed to see if children with similar acceptability ratings choose to pair up for interviews and if this has any impact on data collected during interviews.

10. REGULATORY & ETHICAL ISSUES

10.1. Ethics

10.1.1. Risks and benefits for trial participants and society

The proposed trial does not pose any substantial ethical issues. We plan to test two established clinical technologies. There is no placebo control arm and hence all children participating will receive a treatment of clinical benefit. The question to be answered by the research is which technology is more effective from a clinical and cost-effectiveness perspective.

The placement of PFS is more complex and requires more interventional procedures compared with FV. Knowing the relative costs of these technologies in the short term will provide guidance to the NHS in the development of community based prevention.

From a societal perspective, the cost of treating dental caries poses a substantial burden on the NHS and individuals throughout life. Avoiding the pain and suffering associated with the sequelae of dental caries is desirable, as is avoiding the impact of dental disease on the quality of life of affected individuals. Dental restorations in permanent teeth in childhood require maintenance throughout life. The outcome of this trial has the potential to benefit both those participating and by extrapolation the one in three children in Great Britain who have experienced dental decay by age 11 years.

For participants receiving either the PFS or FV, preventing dental caries in their first permanent molar teeth outweighs the risk of the potential side effects from either treatment. FV application is not recommended in children with severe allergic tendencies (i.e. those who have previously been hospitalised for asthma). We will actively seek out and exclude such children from the study (see exclusion criteria).

The trial treatments will be delivered by appropriately trained and experienced clinical staff subject to NHS clinical governance arrangements overseen by the Cardiff and Vale UHB.

10.1.2. Research Ethics Committee (REC)

This study protocol will be submitted to a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority (UKECA) for review and approval. A favourable ethical opinion must be obtained from the REC before commencement of any trial procedures (including recruitment of patients) occurs.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS R&D (and MHRA approval if applicable to the amendment). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 days of completion of the last patient's final study procedures. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 days.

A summary of the Clinical Trial Report will be submitted to the REC responsible for the study within one year of completion of the last subject's final study procedures.

10.1.3. Ethical Conduct of the Study

The Co-Chief Investigators shall be responsible for ensuring that the clinical study is performed in accordance with the following:

- Declaration of Helsinki (Seoul, 2008; Appendix 8).
- ICH Harmonised Tripartite Guideline for Good Clinical Practice.
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) as amended by the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 (Statutory Instrument 2006 No. 1928 and No. 2984) and Amended Regulations 2008 (Statutory Instrument 2008 No. 941).
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2nd Edition, September 2009 and Department of Health 2nd Edition, July 2005)

10.1.4. Patient Information and Consent

The parent/person with parental responsibility for children invited to participate in the study will be informed of the nature, extent, design and conduct of the study and their consent for admission of the child for which they have parental responsibility will be obtained in writing prior to any-trial specific procedures being performed. They will be given the opportunity to ask questions and will be informed of their right to withdraw the child from the study at any time, for any reason. The procedure by which informed consent will be obtained is described in further detail in Section 5.6.

10.2. Clinical Trials Authorisation (CTA)

This clinical trial has been registered in the EudraCT database and a Clinical Trials Authorisation (CTA) will be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA) prior to the start of the study in accordance with Part 3, Regulation 12 of the UK Statutory Instrument.

10.3. Trial monitoring

Regular monitoring will be performed according to ICH GCP and the trial monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

10.4. Data storage & retention

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network.

10.5. Trial closure

For the purpose of regulatory requirements the end of the trial is defined as the date of the last treatment visit for the last participant undergoing protocol treatment.

For the purpose of the research ethics committee the study end date is deemed to be the date of last data capture.

10.6. Confidentiality

The Chief Investigator, CDS staff and the Seal or Varnish study team will preserve the confidentiality of participants in accordance with the Data Protection Act 1998. All data will be handled according to the principles of the Data Protection Act, especially for sensitive, personal data. Data will be anonymised and stored on a password protected computer located in secure University buildings and appropriately backed up. Any data transfer will be closely monitored. A privacy risk assessment will proactively identify and ameliorate risks of breaches of confidentiality and clearly designate the named individuals who will be allowed to access identifiable information. All data will be retained for up to 15 years post study closure in line with Cardiff University's procedures.

10.7. Funding

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (HTA ref: 08-104-04).

Participating schools will receive a payment of £200 to reimburse for any increased demand on staff/time resources compared with the existing Designed to Smile programme.

10.8. Audits & inspections

The trial is participant to inspection by the NIHR as the funding organisation. The study may also be participant to inspection and audit by Cardiff University under their remit as sponsor.

As this trial is classified as a clinical trial of investigational medicinal products (CTIMP), it may also be participant to inspection by the MHRA.

11. TRIAL MANAGMENT & QUALITY ASSURANCE

11.1. TSC (Trial Steering Committee)

A TSC will be established and will meet at least annually. It will comprise an independent chair and five other independent members. This committee will provide independent oversight of the study and all appropriate disciplines have been covered in choosing TSC members. The committee will be chaired by Prof Lorna Macpherson (Professor of Dental Public Health, University of Glasgow) who has extensive clinical trials expertise. Members will be Mr David Thomas (Consultant in Dental Public Health, National Public Health Service for Wales / Acting Chief Dental Officer, Welsh Assembly Government), Prof Nicky Kilpatrick (Professor of Paediatric Dentistry, University of Bristol), Dr Tanya Walsh, (Lecturer in Dental Statistics, University of Manchester), Mrs Nicola Williams (Headteacher, Deri Primary School, Bargoed), and a service user representative. The Co-chief Investigators (IC/BC), trial statisticians (KH/RP), trial manager (SH) and acting CDS director (CH) will be in attendance. The first meeting will be before the trial commences to review the protocol and arrange the timelines for the subsequent meetings. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC.

11.2. IDMC (Independent Data Monitoring Committee)

In order to monitor accumulating data on patient safety and treatment benefit an independent data monitoring committee (IDMC) will be established. The DMC will act as an advisory body to the TSC and will meet annually. Membership will comprise Prof Helen Worthington (Professor of Evidence Based Care, University of Manchester) who has extensive experience of clinical trials, Prof Chris Deery (Professor of Paediatric Dentistry, University of Sheffield) and a service user representative.

11.3. Trial Management Group (TMG)

The TMG will consist of the Co-chief Investigators, Co-Applicants, a member of the CDS team, a service user representative, Trial Manager, Trial Statistician and Trial Secretary. The role of the TMG will be to help set up the study by providing specialist advice, input to and comment on study procedures and documents (information sheets, protocol, etc). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will meet monthly throughout the course of the study.

11.4. Internal Project Team

This group will consist of the Co-chief Investigators and the Trial Management Team within SEWTU and will meet at least fortnightly to discuss the day-to-day issues that arise from the study. All important discussions will be relayed to the TMG for final decision.

11.5. Trial Documentation and data

Electronic data will be stored on fire-walled University computers, and only accessible to researchers involved in the study. All procedures for data storage, processing and management will be in compliance with the Data Protection Act 1998. All paper records will be stored in a locked filing cabinet, with keys available only to the trial management team. The trial statistician will carry out analysis. All essential documents generated by the trial will be kept in the trial master file.

12. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the study's publication policy.

13. MILESTONES

The trial will last 48 months, commencing formally on 1st April 2011 (5 months set-up, 4 year and 3 month clinical phase, 4 months analysis and write-up). Timing is dictated by the school year and the need for 920 study participants to be assessed/treated twice per annum. The original aim was to recruit all 920 participants within one school year, however recruitment during the first school year did not reach the target of 920; for this reason, the decision to extend recruitment to a second cohort from the next school year was made by the Trial Management Group (supported by the Independent Data Monitoring Committee, Trial Steering Committee and trial funder [NIHR]). A Gantt chart outlining the study timetable is at Appendix 9. The key study milestones are as follows:

- Prior to 1st April 2011 – Favourable ethical opinion received from REC; notice of acceptance for CTA received from MHRA; NHS R&D approval received.
- April – September 2011: Recruitment of schools and participants
- September – December 2011: Baseline assessments and initial application of PFS/FV for Cohort 1
- September – December 2011: Baseline assessments and initial application of PFS/FV for Cohort 2
- September – December 2012 & 2013: Annual caries assessments for Cohort 1
- September – December 2013 & 2014: Annual caries assessments for Cohort 2
- September – December 2014: Final outcome assessments (clinical and non-clinical) for Cohort 1
- September – December 2015: Final outcome assessments (clinical and non-clinical) for Cohort 2
- January – March 2016: Statistical analysis and report preparation
- Prior to 31st March 2016: Delivery of final report to HTA and dissemination of results

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15. APPENDICES

Appendix 1- Cardiff and Vale UHB CDS clinical protocol for application of Delton® Pit and Fissure Sealant

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Cardiff and Vale University Health Board

It is necessary to remove plaque and debris from the enamel and the pits and fissures of the tooth. Any debris that is not removed will interfere with the proper etching process and the sealant penetration into the fissures and pits. Children who are to have fissure sealant applied should brush their teeth / have their teeth brushed with a toothbrush beforehand.

Risk Assessment

This risk assessment reduces the possibility of children with oral/ facial infections being included.

The risk assessment is carried out **BEFORE** the application procedure is started. This is to ensure that any child with any abnormality of the lips, face or soft tissues of the mouth is excluded. Children who are showing obvious signs of systemic illness e.g. colds, 'flu, chicken pox etc should also be excluded on that day.

The Risk Assessment should be carried out as follows:

The Extra-Oral Assessment

- Check the skin of the face and around the mouth for abnormalities (spots, inflammation, swelling etc)
- Check the lips for lesions/ infections

The Intra-Oral Assessment

- Check the right and left inner cheeks and the insides of the lips using the disposable mirror provided in the pack
- Check the top and underneath the tongue.

The teeth and gums should be checked for signs of decay and/ or infection in the following order:

- Check the upper right teeth and gums
- Check the upper left teeth and gums
- Check the lower right teeth and gums
- Check the lower left teeth and gums

If everything appears normal the fissure sealant may be applied. Children with abnormalities of the skin around the mouth, lips (e.g. cold sores), or soft tissue lesions should not have the fissure sealant applied.

If the child has any abnormality of the lips or mouth, they should be referred for a dental opinion.

The Application Procedure

Once the risk assessment has been carried out, the application procedure can begin. If a child gets upset or protests during any part of the procedure, the procedure should be abandoned.

Step 1: Isolate the tooth/teeth

- It is absolutely imperative to keep the tooth free from salivary contamination
- Use dry guards, cotton wool rolls or saliva ejectors to aid moisture control

Step 2: Dry the surfaces

Step 3: Etch the surfaces

- The etchant should be applied to all the pits and fissures. In addition, it should be applied at least a few millimeters beyond the final margin of the sealant and in accordance with manufacturer directions
- Do not allow the etchant to come into contact with the soft tissue. If this occurs, rinse the soft tissue thoroughly

Step 4: Rinse and dry the tooth/teeth

- Rinse all the etchant material from the tooth in accordance with manufacturer directions
- The tooth is dried until it has a chalky, frosted appearance. If it does not, the tooth should be re-etched in accordance with manufacturer directions. It is imperative to avoid salivary contamination. There is agreement that moisture contamination at this stage of the process is the most common cause of sealant failure

Step 5: Apply the material and evaluate for voids, marginal discrepancies or retention problems

- Be careful not to incorporate air bubbles in the material
- Follow protocol for light cured dental sealant material in accordance with manufacturer directions
- After the sealant has set, the operator should wipe the sealed surface with a wet cotton pellet. This allows for the removal of the air-inhibited layer of the non-polymerized resin. Failure to perform this step may leave an objectionable taste in the child's mouth

Step 6: Evaluate the sealant

- The sealant should be evaluated visually and tactically. Attempt to dislodge it with a probe
- If there are any deficiencies in the material, more sealant material should be applied

Step 7: Evaluate the occlusion

- Unfilled resins will wear down naturally and do not require occlusal adjustment

Step 8: End of Procedure

- Reward child with a motivation sticker

Appendix 2 - Cardiff and Vale UHB CDS clinical protocol for application of Duraphat® Fluoride Varnish

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Cardiff and Vale University Health Board

Risk Assessment

This risk assessment reduces the possibility of children with oral/ facial infections being included.

The risk assessment is carried out **BEFORE** the application procedure is started. This is to ensure that any child with any abnormality of the lips, face or soft tissues of the mouth is excluded. Children who are showing obvious signs of systemic illness e.g. colds, 'flu, chicken pox etc should also be excluded on that day.

The Risk Assessment should be carried out as follows:

The Extra-Oral Assessment

- Check the skin of the face and around the mouth for abnormalities (spots, inflammation, swelling etc)
- Check the lips for lesions/ infections

The Intra-Oral Assessment

- Check the right and left inner cheeks and the insides of the lips using the disposable mirror provided in the pack
- Check the top and underneath the tongue.

The teeth and gums should be checked for signs of decay and/ or infection in the following order:

- Check the upper right teeth and gums
- Check the upper left teeth and gums
- Check the lower right teeth and gums
- Check the lower left teeth and gums

If everything appears normal the varnish may be applied. Children with abnormalities of the skin around the mouth, lips (e.g. cold sores), or soft tissue lesions should not have the varnish applied.

If the child has any abnormality of the lips or mouth, they should be referred for a dental opinion.

Safety

Children should not take fluoride supplements on the day before, of or following varnish application.

There should be no opportunity for child to ingest more than a single dose.

In the mixed dentition, the recommended dose is 0.4ml.

Acute fluoride toxicity causes nausea and vomiting. If suspected, give milk to drink and arrange for immediate transfer to A&E.

The Application Procedure

1 The teeth should be 'toothbrush' clean prior to application of varnish

2 Gently retract the cheek using a finger or disposable mirror

3 Dry the tooth to be treated using a cotton wool roll

4 Place the cotton wool roll in the buccal sulcus

5 Apply a thin layer of varnish to pits, fissures and smooth surfaces of first permanent molars using a disposable microbrush

6 Remove cotton wool roll

7 Repeat in all remaining quadrants

8 Advise the child not to eat or drink for 30 minutes and not to brush their teeth for 4 hours after application

9 Reward child with a motivation sticker

Appendix 3 – Dental Health Postal Questionnaire (incorporating Caries Risk-Related Habits and Parental Resource Utilisation Questionnaire)

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SEAL OR VARNISH | CARDIFF UNIVERSITY | PRIFYSGOL CAERDYDD

office use only

i. School ID: ☐☐ ii. Participant ID ☐☐☐ iii. Timepoint: Baseline ☐ 12 mo ☐ 24 mo ☐ 36 mo ☐

Seal or Varnish Study – Dental Health Questionnaire

Dear Parent,

Please answer the following questions relating to your child's dental health. The questionnaire is split into 2 parts: Part A relates to your child's normal dental routine and Part B relates to how much of your time is taken up looking after your child's dental health

Thank you very much for taking the time to complete this questionnaire.

PART A: Your child and their normal dental routine

1 Please confirm the following information about your child:

a. your child's initials: ☐☐☐☐

b. your child's date of birth:

Day: ☐☐ Month: ☐☐ Year: ☐☐☐☐

c. your child's gender: Male ☐ Female ☐

2 How often does your child brush their teeth?

Tick one box only

a. Less than once a day ☐
b. Once a day ☐
c. Twice a day ☐
d. More than twice a day ☐
e. Never ☐ skip to ------> 7

3 Who typically carries out the toothbrushing?

Tick one box only

a. The child on their own ☐
b. The child, observed by adult ☐
c. Adult brushes the child's teeth ☐

4 What type of toothpaste does your child usually use?

Tick one box only

a. Normal family toothpaste ☐
b. Children's toothpaste ☐
c. Other (fill in below) ☐

5 How much toothpaste does your child usually use when brushing?

Tick one box only

a. A smear on the brush ☐
b. A pea-sized amount ☐
c. Cover the brush bristles ☐

6 At what age did your child start tooth brushing?

Write age in the box below

_____ Years _____ Months

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7 Is your child currently using any of the following?

Tick as many as apply

	Yes	No	Brand?
a. Mouthwash	☐	☐	.....
b. Fluoride tablets	☐	☐	
c. Fluoride drops	☐	☐	

8 Has your child ever had fluoride varnish or gel applied by their dentist?

Tick one box only

a. Yes ☐
b. No ☐
c. Don't know ☐

9 Does your child attend a dentist for check-ups?

Tick one box only

a. Yes ☐
b. No ☐ skip to ---------> 11

10 How often does your child normally see the dentist?

Tick one box only – fill in months if applicable

a. Every ____ months ☐
b. Only when in pain ☐

11 Has your child lived in South Wales all their life?

Tick one box only

a. Yes ☐
b. No ☐

12 How often does your child eat or drink the following?

Tick one box in each row

	Never	<1 per week	2-3 times per week	4-6 times per week	1 per day	2-3 times per day
a. Milk	☐	☐	☐	☐	☐	☐
b. Water	☐	☐	☐	☐	☐	☐
c. Fizzy drinks	☐	☐	☐	☐	☐	☐
d. Squash	☐	☐	☐	☐	☐	☐
e. Fruit juice	☐	☐	☐	☐	☐	☐
f. Diet / light drinks / low-sugar squash	☐	☐	☐	☐	☐	☐
g. Sweets/confectionary	☐	☐	☐	☐	☐	☐
h. Chocolate	☐	☐	☐	☐	☐	☐
i. Crisps	☐	☐	☐	☐	☐	☐
j. Fruit e.g. apples, bananas	☐	☐	☐	☐	☐	☐
k. Biscuits and cakes	☐	☐	☐	☐	☐	☐
l. High fibre/low sugar breakfast cereals, like porridge, weetabix and shredded wheat	☐	☐	☐	☐	☐	☐
m. Other breakfast cereals, like Crunchy Nut Cornflakes, Frosties, Coco Pops	☐	☐	☐	☐	☐	☐

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PART B: Time taken up looking after your child's dental health

13 **Not counting the mobile dental clinic at your child's school, have you attended any other dental appointments in the last 12 months?**

Tick one box only

a. Yes	☐	*How many times?* _____
b. No	☐	skip to ---------> 15

14 **For each appointment in the last 12 months, please list the following:**

Tick one box in each column

		Appointment #1	Appointment #2	Appointment #3	Appointment #4
(a)	What was the reason for your appointment?	Toothache ☐	Toothache ☐	Toothache ☐	Toothache ☐
		Check-up ☐	Check-up ☐	Check-up ☐	Check-up ☐
		Filling ☐	Filling ☐	Filling ☐	Filling ☐
		Extraction ☐	Extraction ☐	Extraction ☐	Extraction ☐
		Other *(write below)* ☐	Other *(write below)* ☐	Other *(write below)* ☐	Other *(write below)* ☐
		_____	_____	_____	_____
(b)	Where did you receive the treatment?	Family dentist ☐	Family dentist ☐	Family dentist ☐	Family dentist ☐
		Emergency dentist ☐	Emergency dentist ☐	Emergency dentist ☐	Emergency dentist ☐
		Hospital dentist ☐	Hospital dentist ☐	Hospital dentist ☐	Hospital dentist ☐
		Doctor ☐	Doctor ☐	Doctor ☐	Doctor ☐
		Other *(write below)* ☐	Other *(write below)* ☐	Other *(write below)* ☐	Other *(write below)* ☐
		_____	_____	_____	_____
(c)	How many minutes did the appointment take, including travel time?	_____	_____	_____	_____
(d)	How many miles did you have to travel to the appointment?	_____	_____	_____	_____
(e)	How did you travel to the appointment?	Car ☐	Car ☐	Car ☐	Car ☐
		By foot ☐	By foot ☐	By foot ☐	By foot ☐
		Taxi ☐	Taxi ☐	Taxi ☐	Taxi ☐
		Bus ☐	Bus ☐	Bus ☐	Bus ☐
		Train ☐	Train ☐	Train ☐	Train ☐
(f)	Did you have to take time off paid work?	Yes ☐	Yes ☐	Yes ☐	Yes ☐
		No ☐	No ☐	No ☐	No ☐

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15 Has your child been prescribed (e.g. by a dentist/GP) any medicines for tooth related problems?

Tick one box only

a. Yes ☐
b. No ☐ skip to ------> 17

16 What was the medicine that was prescribed?

Tick as many as apply

	Yes	No	How many times?
a. Pain relief medication (Calpol, Junior Ibruprofen)	☐	☐	
b. Antibiotics	☐	☐	
c. Other (write below)	☐	☐	

17 Over the past 12 months have you self-treated your child (without going to the dentist/GP) for a dental problem?

Tick one box only

a. Yes ☐
b. No ☐

If yes, please specify the treatment given:

c. Painkillers ☐
d. Other (write below) ☐

18 Approximately how many days do you think your child has lost from school over the last 12 months due to dental problems and/or dental visits?

Write number of days in box below

_____ days

19 Did you or another carer need to take time off paid work or find yourself unable to undertake normal daily activities because of your child's dental problems or visits?

Tick one box only

a. Yes ☐
b. No ☐

20 Could you describe the present occupation of the child's main parent(s) or carer(s)?

Write in box below

Appendix 4 - Child Health Utility 9D questionnaire

GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Caerdydd a'r Fro | Cardiff and Vale University Health Board | SEAL OR VARNISH | CARDIFF UNIVERSITY | PRIFYSGOL CAERDYDD

For office use only

i. School ID: ☐☐ ii. Participant ID ☐☐☐ iii. Timepoint: Baseline ☐ 12 mo ☐ 24 mo ☐ 36 mo ☐

Seal or Varnish Study - 'Child Health Utility' Questionnaire

Dear Parent,

Please ask your child to answer the following questions. You may help your child if needed, but the answers should be **from the child's point of view**.

Before asking your child the questions, please confirm the following information:

1. **Child's Initials:** ☐☐☐☐
2. **Child's Date of Birth (dd/mm/yyyy)** ☐☐ ☐☐ ☐☐☐☐
3. **Gender:** **Male** ☐ **Female** ☐

These questions ask about how you are today. For each question, read all the choices and decide which one is most like you today. Then put a tick in the box next to it like this þ. Only tick one box for each question.

Example
Today I feel quite upset so I will tick this box:

Upset
- ☐ I don't feel upset today
- ☐ I feel a little bit upset today
- ☐ I feel a bit upset today
- ☑ I feel quite upset today
- ☐ I feel very upset today

Now think about and answer the rest of the questions below

A. Worried
- ☐ I don't feel worried today
- ☐ I feel a little bit worried today
- ☐ I feel a bit worried today
- ☐ I feel quite worried today
- ☐ I feel very worried today

B. Sad
- ☐ I don't feel sad today
- ☐ I feel a little bit sad today
- ☐ I feel a bit sad today
- ☐ I feel quite sad today
- ☐ I feel very sad today

C. Pain
- ☐ I don't have any pain today
- ☐ I have a little bit of pain today
- ☐ I have a bit of pain today
- ☐ I have quite a lot of pain today
- ☐ I have a lot of pain today

D. Tired
- ☐ I don't feel tired today
- ☐ I feel a little bit tired today
- ☐ I feel a bit tired today
- ☐ I feel quite tired today
- ☐ I feel very tired today

E. Annoyed

- ☐ I don't feel annoyed today
- ☐ I feel a little bit annoyed today
- ☐ I feel a bit annoyed today
- ☐ I feel quite annoyed today
- ☐ I feel very annoyed today

F. School Work/Homework (such as reading, writing, doing lessons)

- ☐ I have no problems with my schoolwork/homework today
- ☐ I have a few problems with my schoolwork/homework today
- ☐ I have some problems with my schoolwork/homework today
- ☐ I have many problems with my schoolwork/homework today
- ☐ I can't do my schoolwork/homework today

G. Sleep

- ☐ Last night I had no problems sleeping
- ☐ Last night I had a few problems sleeping
- ☐ Last night I had some problems sleeping
- ☐ Last night I had many problems sleeping
- ☐ Last night I couldn't sleep at all

H. Daily routine (things like eating, having a bath/shower, getting dressed)

- ☐ I have no problems with my daily routine today
- ☐ I have a few problems with my daily routine today
- ☐ I have some problems with my daily routine today
- ☐ I have many problems with my daily routine today
- ☐ I can't do my daily routine today

I. Able to join in activities (things like playing out with your friends, doing sports, joining in things)

- ☐ I can join in with any activities today
- ☐ I can join in with most activities today
- ☐ I can join in with some activities today
- ☐ I can join in with a few activities today
- ☐ I can join in with no activities today

When completed please return to the SEWTU Office using the pre-paid envelope provided.

Thank you very much !

For SEWTU office use only

Received: ☐☐ ☐☐ ☐☐☐☐	Entered into database: ☐☐ ☐☐ ☐☐☐☐
Received by (initials): ☐☐☐	Entered by (initials): ☐☐☐

Appendix 5 - Modified Delighted-Terrible Faces Scale

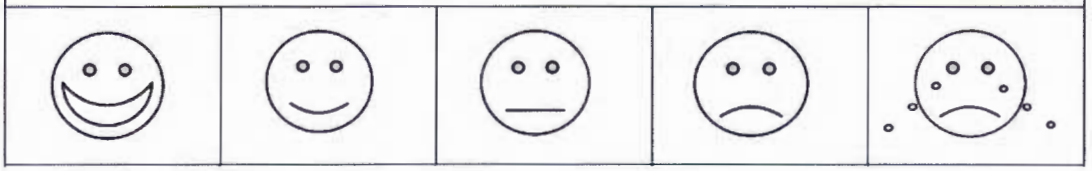
How did you feel during the treatment?

If you had to have the treatment tomorrow, how would you feel?

How do you feel about the time it took to have the treatment?

How did you feel about the taste of the treatment?

How much did you feel like being sick during the treatment?



Appendix 6 - Patient Acceptability Observational Scale

1 Adverse Outcomes Observed

Tick one box in each row

	Yes	No
Vomiting	☐	☐
Gagging	☐	☐
Crying	☐	☐
Excessive arm movements	☐	☐
Excessive leg movements	☐	☐
Other signs of distress (specify below)	☐	☐

2 Time taken to perform the application

Please list the number of minutes and seconds from when the child was seated for the procedure until the child was able to leave the dental chair

_____ Minutes

_____ Seconds

Appendix 7 - ICDAS Training and Calibration Protocol

A. Summary

This protocol describes the training and calibration of dental examiners who will undertake clinical assessments as part of the Seal or Varnish Clinical Trial. These examiners will be experienced Community Dental Officers, employed by Cardiff and Vale University Health Board with substantial clinical experience of the examination of young children. A Training and Calibration exercise will be undertaken on four occasions during the study at baseline before the baseline clinical assessment and at 12, 24 and 36 months ahead of the caries assessments.

B. Aim

To train two dentists involved in the caries assessment to use the ICDAS caries assessment.

C. Training of dental examiners

- The Training and Calibration will be based on British Association for the Study of Community Dentistry (BASCD) Training and Calibration Guidance[1] with substitution of the International Caries Detection & Assessment System (ICDAS). [2]
- Training will involve an online International Caries Detection & Assessment System (ICDAS) [2] training package and a training day. Examiners and recorders will be given access to the training package ahead of the training day to give them the opportunity to familiarise themselves with all aspects of the criteria and conventions prior to the start of the training day. The training day will be lead by Professor Christopher Deery (University of Sheffield) an experienced ICDAS examiner. It will involve a seminar to review the criteria followed by caries assessments of twenty 6-7 year old primary school children from a Community First school in South Wales to practice use of the criteria. A formal Calibration carried out on ten different children will be undertaken after the practice examinations.

D. Recruitment of children for training purposes

- Recruitment of children for the training exercise will take place in a Community First school in South Wales once agreement has been obtained from the head teacher. A letter to head teachers is included (Section M). The school used for the Training and Calibration exercise will not be used in the main study.
- Written consent will be obtained for the children to be examined as part of the training course. A letter will be sent (via the school) to the parents of children aged 6-7 years ages and positive consent obtained for them to take part. A letter / consent form for parents is attached (Section L).

- Sufficient children (30-35) will be recruited for the training session to ensure that they are not examined continuously. If any child does not wish to participate on the day or becomes tired, another will be substituted.

E. Conduct of Dental Examination

- Dental examinations will be conducted within the schools using conventional dental epidemiological survey techniques in line with British Association for the Study of Community Dentistry -co-ordinated surveys.[2]
- The examiner will be seated behind the subject who will be in a supine position on a table or reclined sun-lounger.
- Children will be given a new, sterile toothbrush of appropriate size and asked to brush their teeth. No toothpaste will be used and the toothbrush will immediately be discarded and treated as clinical waste. This aspect of the examination is necessary to allow visualisation of the tooth surfaces to record dental caries in its earliest stages (enamel caries). In the event that plaque or food debris remains adherent, supragingival deposits will be removed by the dentist using either a toothbrush or probe.

F. The examination equipment

- A purpose built light yielding 4000 lux at 1 metre (e.g. Daray) or a similar protected light source will be used for illumination.
- Extension flex and plug adapter for use when necessary with the lamp.
- Disposable paper roll for laying out instruments.
- Materials to ensure cross-infection control including containers for clean instruments, containers for dirty instruments, disinfectant spray/wipes, clean latex-free gloves, eye protection for subjects, clinical waste bags together with sufficient cotton wool buds/rolls etc. for each child.
- Examiners will wear a fresh pair of gloves for each examination.
- Diagnoses will be visual using a plane mouth mirror. A blunt ball-ended probe (CIPTN) with an end diameter of 0.5mm will be used as described below.
- All necessary steps must be taken to prevent cross-infection. A fresh set of previously sterilised instruments will be used for each subject.

G. Examination procedure

- Data will be recorded onto a paper chart chairside.
- Teeth will be examined for caries in the following order:
  (a) Upper Left to Upper Right
  (b) Lower Right to Lower Left
- Surfaces will be examined in the following order:-
  - Distal, Occlusal, Mesial, Buccal, Lingual
- Each tooth will be identified and each surface recorded according to the diagnostic criteria for caries.
- Presence or absence of sepsis in the mouth will be noted and coded.
- If a primary tooth is missing, the state of the permanent successor will be recorded. In cases where both the primary tooth and its permanent successor are present further details will be recorded for the permanent tooth only.

- A tooth is deemed to be present if any part of it is visible.

H. Caries Criteria (ICDAS)

- The ICDAS detection codes for coronal caries range from 0 to 6 depending on the severity of the lesion. There are minor variations between the visual signs associated with each code depending on a number of factors including the surface characteristics (pits and fissures versus free smooth surfaces), whether there are adjacent teeth present (mesial and distal surfaces) and whether or not the caries is associated with a restoration or sealant. Therefore, a detailed description of each of the codes is given under the following headings to assist in the training of examiners in the use of ICDAS: Pits and fissures; smooth surface (mesial or distal); free smooth surfaces and caries associated with restorations and sealants (CARS). However, the basis of the codes is essentially the same throughout:

Code	Description
0	Sound
1	First Visual Change in Enamel (seen only after prolonged air drying or restricted to within the confines of a pit or fissure)
2	Distinct Visual Change in Enamel
3	Localized Enamel Breakdown (without clinical visual signs of dentinal involvement)
4	Underlying Dark Shadow from Dentin
5	Distinct Cavity with Visible Dentin
6	Extensive Distinct Cavity with Visible Dentin

- ICDAS two-digit coding method. A two-number coding system is suggested to identify restorations/sealants with the first digit, followed by the appropriate caries code, for example a tooth restored with amalgam which also exhibited an extensive distinct cavity with visible dentin would be coded 4 (for an amalgam restoration) 6 (distinct cavity), an unrestored tooth with a distinct cavity would be 06. The suggested restoration/sealant coding system is as follows:

0 = Sound: i.e. surface not restored or sealed (use with the codes for primary caries)
1 = Sealant, partial
2 = Sealant, full
3 = Tooth colored restoration
4 = Amalgam restoration
5 = Stainless steel crown
6 = Porcelain or gold or PFM crown or veneer
7 = Lost or broken restoration

8 = Temporary restoration
9 = Used for the following conditions
96 = Tooth surface cannot be examined: surface excluded
97 = Tooth missing because of caries (tooth surfaces will be coded 97)
98 = Tooth missing for reasons other than caries (all tooth surfaces will be coded 98)
99 = Unerupted (tooth surfaces coded 99)

I. Procedure in the event of serious pathology being suspected

- In the course of the training or calibration, an examining dentist may encounter suspected serious pathology (e.g. malignancy). This is very unlikely as the prevalence of such potentially serious pathology is extremely low in this age group. The examination is not a screening exercise and does not involve examination of the oral soft tissues. However, it is possible that such a lesion may be noticed and, as the implications are serious, a protocol to deal with this eventuality is in place.
- In the event that such a lesion is noted, the examiner is obliged to follow a set protocol, which is designed to make sure that the participant's parent or carer is informed, whilst not causing unnecessary worry or alarm.
- The examiner will note the child's name, date of birth and school and will contact one of the survey consultants by telephone, a Consultant in Paediatric Dentistry (Professor Barbara Chadwick). The Consultant will liaise with the examining clinician to obtain parental / carers contact details. Parents will then be contacted by telephone and arrangements made for the child to be seen by their general medical practitioner. A follow-up letter will be sent to the parents/carers and the child's medical practitioner.

J. Data analysis

- A master sheet will be completed for each training session to allow comparison between examiners at the tooth or surface level.
- The number of decayed missing and filled teeth or surfaces each examiner has recorded when examining the same child will be compared to and differences highlighted and discussed.
- For training, no formal statistical analyses will be undertaken and discussions use differences identified from the master sheets and individual charts for instant feedback.
- For calibration ten children will be examined and data entered onto a master sheet.
- Calculation of mean indices (DMFT,FT,dmft,dt) by examiner and the size and direction of the deviation from the benchmark examiner will be compared.
- Subsequently inter and extra examiner agreement will be determined using Kappa statistics.

K. Training and Calibration Protocol References

1. Pine, CM, Pitts, NB, Nugent ZJ. (1997) British Association for the Study of Community Dentistry (BASCD) Guidance on the Statistical Aspects

of Training and Calibration of Examiners for Surveys of Child Dental Health. A BASCD Co-ordinated Dental Epidemiology Programme Quality Standard. Community Dental Health, 14 (Supplement 1), 18-29.

2. International Caries Detection and Assessment System (ICDAS) Coordinating Committee. (2005) International Caries Detection and Assessment System (ICDAS II) Training Manual. http://www.icdasfoundation.dk/

L. LETTER/CONSENT FORM FOR EXAMINATIONS FOR TRAINING

<<To be produced on appropriate headed paper>>

Professor I.G. Chesnutt
Tel: 029 2074 2447 / 6680

[DATE]

Dear Parent/Guardian

The National Health Service has commissioned a study looking at the two different ways of preventing tooth decay in children between the ages of 6 and 7 years.
Before the study begins, it is important to train the dentists taking part and *(insert school)* has been chosen as the school where the training will take place.
I have spoken to *(head teacher* and *)* is happy for children from *(school)* to take part in this study, but we also need your consent. I should be grateful if you would allow your child to take part in the training programme which will take place on .
This will involve a simple dental examination carried out by three dentists at *(school)* and will take up no more than an hour of school time.
This is not part of the normal school dental inspection and no treatment or recommendations for treatment will be carried out.
If you would like more information, please contact me on (029 2074 2447 / 6680) and I will be happy to discuss it with you. If you are willing to allow your child to take part, please complete the slip below and return it to school **as soon as possible.**

Thank you for your help

Yours faithfully

Professor I Chestnutt

School: .....

Child's name: ..... Age: ..... Class: .....

I am willing to allow my child to take part in the dental training exercise.

Signed: ..... Parent/Guardian Date: .....

M. LETTER TO THE HEADTEACHER OF SELECTED SCHOOL

<<To be produced on appropriate headed paper>>

Professor I.G. Chestnutt

Tel:

[DATE]

Dear Headteacher,

RE: Seal or Varnish a Clinical Trial – Pilot study

The National Health Service (Health Technology Assessment division) have commissioned a clinical trial to test two different methods of protecting children's teeth. The study is being carried out by the Cardiff University School of Dentistry. It will involve 920 children from Community First schools in South Wales aged between 6 and 7 years and the start of the study and follow them for thirty six months. The study will help to identify the best way of protecting the childrens' teeth from tooth decay.

The first stage of the study involves piloting the methods that will be used in the mainstage of the study. We hope that you will agree to let your school take part in the Pilot study to do this. We need to identify approximately 35 children aged between 6 and 7 years whose parents will consent to their child undergoing a dental examination.

Parent/guardians of children aged 6 to 7 will be sent a letter explaining the study and asking them to allow their child to take part in the study and undergo a short dental examination.

When the dentist visits the school they will require a room in which to carry out the examinations and some assistance in bringing the selected children to the room to be examined. The school will also need to keep a list of any children whose parents withdraw them from the study to give to the dentist when they visit the school.

I appreciate schools have many demands on their time but I hope you will feel able to help us. Participation in the study is voluntary. The dental visits are planned for the <<insert date>>. If you are able to take part please return the attached slip in the envelope provided so that I can arrange a date for the dentist to visit.

If you have any queries about the survey, please contact me, Professor Ivor Chestnutt on 029 2074 2447 / 6680.

Thank you.

Yours sincerely

Professor Ivor Chestnutt

School: .....

I am willing to allow my school to take part in the dental training exercise.

Signed: ..... Head Teacher Date: .....

Appendix 8 - Declaration of Helsinki

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
53rd 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 serious adverse events. 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

Appendix 9 - Gantt chart for study