Cardiff Risk Assessment Form (RAF) for CTIMPs

This Risk Assessment Form (RAF) should be completed by the Chief Investigator for all CTIMPs Sponsored by Cardiff University (CU).

A flow chart of the procedure for completing the RAF is presented in Appendix 1. The RAF may be completed in conjunction with the CU Research Governance Coordinator. The RAF will then be reviewed by the Sponsor Assessment Meeting (SAM) where required. Following review and completion of any necessary amendments the RAF will be signed by the CI, Trials Unit and Sponsor.

Study Title (in full):	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		
Short title:	Seal or Varnish?		
EudraCT No:	2010-023476-23	**Name of CI:**	Prof. I. G. Chestnutt
Sponsor No:	SPON766-09	**Employer of CI:**	Cardiff University
Proposed Sponsor Organisation:	☒ Cardiff University ☐ Other (please state)……..		
Risks associated with trial IMP/interventions: ☒ **Type A** = Comparable to the risk of standard medical care ☐ **Type B** = Somewhat higher than the risk of standard medical care ☐ **Type C** = Markedly higher than the risk of standard medical care	**Justification** The two interventions (fissure sealant and fluoride varnish) to be evaluated in the trial are Delton® Light Curing Pit & Fissure Sealant (Dentsply Ltd; CE0086 marked medical device) and Duraphat® 50 mg/ml fluoride dental suspension, (Colgate-Palmolive (UK) Ltd; licenced medicine). Both interventions are standard care for the prevention of dental caries in the target population, and will be used according to their marketing authorisation/manufacturer's instructions.		

Risk/Hazard Area	Risk level • Low (L) • Medium (M) • High (H)	Considerations/Concerns identified Provide details of trial-specific considerations/risk concerns	Management/mitigation strategies • Address all concerns identified • Provide details of any risk-adaptations to conventional GCP management strategies employed • Discuss any impact on trial monitoring requirements
1. RISK TO TRIAL PARTICIPANTS			
1.1 Non-compliance with informed consent process	M	1. Accessibility of information provided to parent in order to make informed decision for child to participate. 2. Willingness/understanding of child regarding participation in trial. 3. Consent provided by parent remotely; no face-to-face informed consent discussion. 4. Consent may be provided by person without legal parental responsibility 5. Child enrolled onto study with insufficient/missing consent	1. Information sheet and informed consent form adapted from NRES in consultation with local parents group representative of target study population. 2. Formal assent not sought due to young age of child at enrolment (6-7 yr old); trial dental staff have considerable experience with children of this age and will not enrol children who are clearly upset/non-compliant or unable to tolerate examination. 3. Remote consent process current practice for existing Community Dental Service programmes; modification for use to obtain trial consent approved by REC; Information sheet encourages parent to contact trial team by telephone to discuss/ask questions if required. 4. Person providing consent verified with school for parental responsibility. 5. Any missing information/ambiguity on consent forms is clarified with parent via telephone prior to enrolment onto trial. 100% monitoring of informed consent at trials unit prior to randomisation onto trial
1.2 Failure to protect participants' privacy	M	1. Process for distribution and collection of invitation packs/consent forms to parents as per current dental programme; school verifies person with parental responsibility has signed consent form. 2. Ambiguity of school's role in trial versus existing programme; potential for breach of confidentiality of trial data.	1. Parents will be advised in the information sheet that certain designated members of school staff will be aware of their child's participation in the trial for the purpose of verifying consent. As the trial is conducted in parallel with existing dental programme; participation in the trial vs. existing programme will not distinguishable by school staff for subsequent examination/ treatment visits. 2. Responsibilities of school clearly described in Trial School Agreement, signed by Head Teacher prior to distribution of invitations to parents. School staff involved only distribution/collection of information sheets/consent forms and verifying parental responsibility; no access to trial data.

1.2 Failure to protect participants' privacy *(continued)*	M	3. Existing dental programme paperwork includes both personal identifiable data and clinical/dental data; potential for confusion over which types of data can be recorded on trial case report forms etc. 4. Parents will be completing questionnaires (collecting health economic and caries-risk data) at home and returning to the trials unit by post. Risk of breach of confidentiality of trial data if post undelivered/intercepted.	3. Case report forms identify participants by anonymised School and Participant ID number only and are designed to minimise risk of identifiable information (e.g. names) being added by trial staff. Importance of maintaining confidentiality of trial-specific documentation included in training provided to all trial staff at site initiation. 4. Postal questionnaires identify participants by anonymised School and Participant ID number only (pre-completed at trials unit prior to distributing questionnaire to parents).
1.3 Hazards of the intervention/IMP *Where risks associated with the intervention are somewhat or markedly higher than the risk of standard care (i.e. Type B or Type C trials), details regarding specific risks to body systems and proposed methods for clinical monitoring of such risks should be described.* Example: Body System: cardiovascular Risk: prolonged QT interval Clinical monitoring: 12 lead ECG at 6, 12 and 24 hours post dose	L	1. Both interventions are clinically effective and are widely used in standard care for the prevention of dental caries; however some contraindications for fluoride varnish (significantly: bronchial asthma). 2. Child's medical history (e.g. development of asthma) may change during course of trial affecting suitability to receive fluoride varnish. 3. While the interventions are considered to be low risk to participants, the below undesirable effects are described: in the SmPC for Duraphat: • Oedematous swelling of the oral mucosa in subjects with tendency to allergic reactions has been observed in exceptional cases • Ulcerative gingivitis and stomatitis have been reported by sensitive individuals. • In rare cases, asthma attacks may occur in patients who have bronchial asthma. • Retching may exceptionally occur after a high dosage and extensive application In patients	1. As per current practice, relevant medical history to determine suitability for treatment with fluoride varnish (including any history of hospitalisation due to allergies or asthma) obtained from parents via Medical History Form included with trial invitation pack distributed to parents. Exclusion criterion 1 excludes children with relevant medical history to preclude fluoride varnish use, which will undergo 100% SDV as part of eligibility monitoring prior to randomisation. 2. Any changes to child's medical history obtained from parent on annual basis via Medical History Update Form. 3. Both interventions are applied as part of standard care, with clearly described local clinical protocols for their application (included as appendices to the trial protocol). All trial staff have considerable experience in the delivery of both interventions and any adverse events will be managed according to established clinical practice. Any adverse reactions observed for either intervention will be treated as per standard care, and only recorded/reported if considered to meet the criteria for a Serious Adverse Event (see item 3.5).

1.3 Hazards of the intervention/IMP *(continued)*		with gastric sensitivity in the manufacturer's instructions for Delton: • reversible inflammatory changes of the oral mucosa • Anaphylactic reactions may occur in susceptible individuals	
1.4 Hazards of trial assessment methods	L	1. Primary outcome measure is assessment of participants' caries status, requiring a comprehensive dental examination. While this is non-invasive, there is a slight risk of some participants experiencing discomfort. 2. Health-related quality of life is evaluated using the Child Health Utility 9 Dimension (CHU-9D) questionnaire. While this questionnaire has been validated for the age range of the trial population, there is a small risk that some questions have the potential to cause upset/distress to children with a difficult home life.	1. Dentists performing trial assessments have considerable experience with trial population age group as part of existing dental programmes; discretion will be exercised as to any discomfort the child may be experiencing. Children who are not able to tolerate the baseline examination will not be enrolled onto the trial. 2. Implementation of the CHU-9D questionnaire in the study population was piloted with a representative group of children and parents to determine the most appropriate way of administering the questionnaire to minimize potential for upset/distress to participants.
1.5 Other *please give details:*	M	1. Potential for additional fluoride to be administered to participant by family dentist/parent	1. Parents advised not to give their child fluoride-containing dental products (other than fluoride toothpaste) for duration of involvement in trial.

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2. VALIDITY OF RESULTS			
2.1 Study inadequately powered (inaccurate recruitment feasibility assessments)	M	1. Little experience recruiting research participants from target population (i.e. children/parents from deprived areas) – risk of insufficient recruitment due to low uptake/consent rate. 2. Insufficient power due to lower than anticipated incidence of disease. 3. Outcome data collected 12, 24 and 36 months subsequent to enrolment; potential risk for missed assessments/loss to follow-up	1. Established relationship between Community Dental Service and schools involved in study; currently very good recruitment rates (>80%) onto existing dental programmes. Trial Information Sheets and consent forms based on current programmes, further developed in consultation with local parents' group representative of target study population to maximise accessibility and understanding. Recruitment closely monitored by Project Team and Trial Management Group in order for any required action to be taken as soon as possible. 2. Reliability of disease incidence estimates based on several years' data collected by Community Dental Service in target population. 3. Sample size calculation accounts for conservative estimates of missed assessments/withdrawals/losses to follow-up. Assessments performed using Mobile Dental Clinical at schools (as per current dental programme), therefore not reliant on parental adherence to assessment schedule/attending individual dental appointments.
2.2 Major Violation of eligibility criteria	M	1. Ineligible participants enrolled onto trial by inexperienced trial staff	1. Dental staff trained in GCP, trial protocol and trial-specific procedures for assessing eligibility of participants. Baseline examination/ screening CRF designed to ensure all eligibility criteria assessed and documented. 100% SDV of eligibility criteria at trials unit prior to randomisation.
2.3 Lack of robust randomisation procedure	L	1. Randomisation of ineligible participants 2. Unbalanced/incorrect randomisation	1. (see item 2.2) 2. Randomisation performed at trials unit by trial statistician. Randomisation program tested prior to trial initiation and all randomisation lists 100% QCd by additional statistician prior to provision to site.

2.4 Unreliable outcome Assessment	L	1. Dental staff inexperienced at collection of clinical trial data	1. Clinical data collection CRFs for primary outcome measure based on established scale (International Caries Detection and Assessment System; ICDAS); dental staff experience in completion of similar data collection tools as part of routine dental surveys. All staff trained on completion of trial CRFs (including GCP aspects) at trial initiation.
		2. Inconsistent caries scoring due to complexity of caries assessment tool and multiple dentists performing assessments.	2. All dentists performing trial caries assessments have extensive experience in the evaluation of caries in the trial population, and will be trained and calibrated in ICDAS scoring (including correct completion of assessment tool) prior to site initiation, and prior to each annual caries assessment during the trial. Inter-examiner variability determined during each calibration exercise, and intra-examiner reproducibility determined via re-examination of 5% of participants during each school examination visit. If agreement between/within assessors is below an acceptable threshold (i.e. kappa statistic <0.7), additional training will be provided. CRFs may also be reviewed to determine if any outliers (e.g. due to difficulty in performing examination) negatively affect the variability.
		3. Insufficient completion/response rates to questionnaires.	As ICDAS charts represent source data, SDV as part of trial monitoring not applicable. 3. Treatment acceptability questionnaires completed at time of treatment on Mobile Dental Clinic and trial staff trained on specific written procedures for completion. Data on dental hygiene behaviour (to determine caries risk habits) and health economics data (parental resource utilisation and quality of life) is collected via postal questionnaires which may result in poor response rates; REC-approved non-conditional incentives will be provided to parents to encourage completion, in addition to telephone follow-up/reminders to parents yet to return questionnaires.
		4. Potential risk of unblinding assessor due to obvious physical difference between sealant and varnish.	4. While there is the potential for the assessing dentist to identify participants who have received sealant, it is unlikely that participants randomised to receive fluoride varnish will be distinguishable from those for whom a previously applied sealant has become dislodged. For this reason the assessor will be considered to be blinded to treatment allocation and will not have access to the randomisation list. The risk of the assessor

2.4 Unreliable outcome Assessment *(continued)*		5. Confounding influence of non-trial sources of fluoride or independent placement of fissure sealant.	becoming unblinded will be acknowledged during discussion of the trial results, but will not impact the statistical analysis performed on the outcome data. 5. Details regarding home dental care regime (including use of fluoride-containing dental products) collected annually from parents via questionnaires to determine caries risk. Participant's dentists (if registered) notified of involvement in trial and requested not to apply fissure sealants or topical fluoride preparations for subsequent 36 months. Parent also advised not to give their child fluoride-containing dental products (other than fluoride toothpaste) for duration of involvement in trial.
2.5 Poor Data Management system	L	1. Inadequate management of trial data 2. Poor data quality and integrity	1. Site and trials unit staff trained on written data management processes (including trial-specific process and data management plan). 2. Data used to determine eligibility/for randomisation subject to 100% monitoring (including SDV where applicable). All other clinical data subject to electronic validation/central monitoring during entry onto trial database. Trial data collection/management overseen by Independent Data Monitoring Committee (IDMC).

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3. TRIAL MANAGEMENT			
3.1 Inexperienced Trial Staff	M	1. Dental staff at research site inexperienced with regards to CTIMPs 2. Principal Investigator (PI) inexperienced with regulatory requirements/maintenance of Investigator Site File (ISF)	1. All site staff will undergo GCP training prior to site initiation, in addition to training on the protocol and associated trial-specific procedures applicable to their role in the trial. All staff are experienced in delivery (and management) of trial interventions as part of standard care. Monitoring of training logs/CVs performed as part of site initiation and as part of routine monitoring visits 2. PI has received GCP training and was closely involved in protocol development and trial set-up. Support and training regarding maintenance of ISF at Community Dental Service Head Office will be provided to PI and senior site staff by trials unit and ISF monitoring will be performed prior to site initiation, and subsequently as part of routine monitoring visits.
3.2 Competence of Partner Organisations	L	1. Potential for misunderstanding of roles and responsibilities between Cardiff University/ trials unit (SEWTU) and Cardiff & Vale UHB Community Dental Service (CDS). 2. Ambiguity with regards to role/responsibility of school versus CDS.	1. Responsibilities of sponsor, SEWTU, CI and PI/site clearly laid out in Memorandum of Understanding, agreed and signed off prior to trial initiation. 2. Role/responsibility of school clearly documented in School Agreement signed prior to distribution of invitation packs to parents. Role/responsibility of CDS documented in site agreement between Cardiff University and CDS. Due to potential issues with schools acting as research sites, as per existing dental programme, involvement of schools limited to identification of potential participants (via provision of class lists to CDS), distribution/collection of invitation packs/consent forms and verification of parental responsibility (see item 1.2).

3.3 Inadequate Trial Management	L	1. Potential for misunderstanding of roles and responsibilities of SEWTU versus site staff 2. Potential for inadequate trial oversight	1. Both site and trials unit delegation logs maintained; role-specific responsibilities detailed in trial-specific SOPs 2. Hierarchy for trial oversight clearly established and documented in protocol and group/committee charters (i.e. Project Team, Trial Management Group, Trial Steering Committee).
3.4 Appropriate resources not available	L	1. Insufficient funding for completion of trial 2. Withdrawal of involvement of trial site 3. Insufficient site staff to perform trial duties in addition to existing dental programme	1. Trial underwent detailed costing exercise by sponsor prior to funding application 2. CDS Director involved in trial design and set-up; contract between sponsor and trial site agreed prior to trial initiation. 3. Funding application included provision of sufficient extra dental staff to accommodate additional trial-related duties
3.5 Inadequate Pharmacovigilance systems	L	1. Site staff inexperienced in Pharmacovigilance (PV) requirements for CTIMPs 2. Potential for inadequate oversight of pharmacovigilance by CI/trial team if frequency of SAE occurrence is low.	1. PV training provided to all staff prior to site initiation, including training on trial-specific PV procedures. Due to low risk nature and extensive clinical experience of trial interventions, justification for adapting the protocol/safety monitoring plan to require reporting to the Sponsor of SAEs only (non-serious AEs managed according to standard care but not recorded as part of trial). This adaptation is still in compliance with UK legislation and is and approved as part of the CTA 2. SAEs reviewed monthly by Trial Management Group and annually by IDMC. Site and trial team trained on trial-specific procedure for reporting SUSARs.
3.6 Poor IMP management systems	L	1. Insufficient management of IMP due to inexperience of site staff with CTIMPs 2. Inadequate IMP labelling and accountability	1. Training on IMP management requirements for CTIMPs (including training on trial-specific IMP management procedures) provided to all staff responsible for handling/managing IMP prior to site initiation. Due to marketing authorisation status of IMP and extensive use as part of standard care by trial site, adaptation of IMP record keeping requirements (i.e. storage temperature logs, detailed accountability logs) implemented to minimise additional IMP management requirements above standard practice. 2. Trial-specific labelling requirements for IMP adapted to allow multiple patient applications from same IMP container. Adequate IMP accountability maintained via central accountability log and inclusion of IMP batch numbers and expiry dates on Treatment CRFs.

3.6 Poor IMP management systems *(continued)*		3. Maintaining IMP in incorrect storage conditions	3. IMP stored in same conditions as per standard practice, but kept separate to non-clinical supplies/medicines. Both products are stable with long shelf lives under standard conditions (room temperature/ below 24 °C) therefore justification for not monitoring IMP storage temperature for trial.
3.7 Influence/interference of private organisation upon trial governance	N/A	Not applicable (No private organisations involved in trial)	Not applicable (No private organisations involved in trial)

For Office Use Only:	
Summary of the main risks and associated mitigation strategies:	

Authorisation: This section is to be signed once all risks and risk management strategies have been agreed

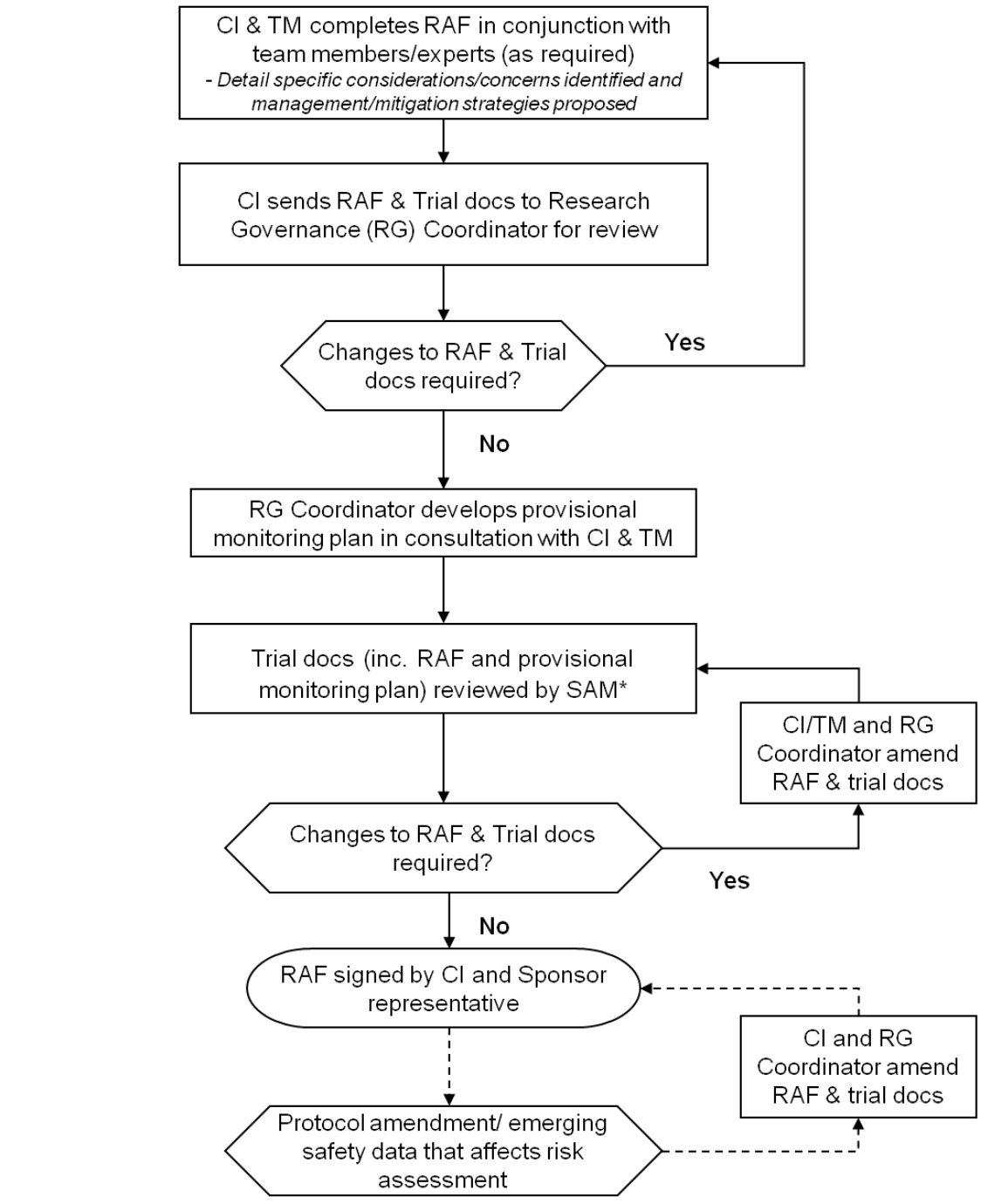
CI/PI
Name
Signature
Date

Sponsor
Name
Signature
Date

Trials Unit Director
Name
Signature
Date

Appendix 1

Procedure for completing Cardiff Risk Assessment Form (RAF) for CTIMPs



*Sponsor Assessment Meeting also reviews protocol, PIL & consent form