### Clinical Investigational Plan (CIP) for Medical Device Studies

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| **Full title of Investigation:** | SMART composite (Self-bonding Material for Atraumatic Restorative Treatment) restoration of children’s primary molar teeth after minimal caries removal: Class IIa device in a single site, single arm study. |
| **Short title:** | SMART filling for caries in primary teeth |
| **Version and date of Clinical Investigation Plan (CIP):** | V2.0 05/7/18 |
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**List of abbreviations**

|  |  |
| --- | --- |
| 4META | 4-MethacryloxyEthyltriMelliticAnhydride - adhesion promoting monomer |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ART | Atraumatic Restorative Treatment – requires minimal carious tooth removal |
| CA | Competent Authority |
| CI | Chief Investigator |
| CIA | Clinical Investigation Agreement |
| CIP | Clinical Investigation Plan |
| CQ | Camphorquinone initiator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| DCF | Data Clarification Form |
| DCP | DiCalcium phosphate - crystalline forms are brushite and monetite |
| DD | Device Deficiency |
| EC | European Commission |
| EDAX | Energy Dispersive X-ray spectroscopy - elemental analysis with SEM |
| EU | European Union |
| EUDAMED | European Medical Devices Regulatory Database |
| FTIR | Fourier Transform infrared spectroscopy |
| GCP | Good Clinical Practice |
| GIC | Glass Ionomer Cement |
| GMP | Good Manufacturing Practice |
| HA | Hydroxyapatite |
| HPLC | High Pressure Liquid Chromatography |
| HRA | Health Research Authority |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| IDMC | Independent Data Monitoring Committee |
| IMD | Investigational Medical Device |
| ISF | Investigator Site File |
| ISO | International Standardisation Organisation |
| JRO | Joint Research Office |
| MA | Marketing Authorisation |
| MCPM | Mono Calcium Phosphate Monohydrate - acidic calcium phosphate |
| MDD (ER) | Medical Device Directive (Essential Requirement) |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NCA | National Competent Authority |
| NHS | National Health Service |
| NHS R&D | National Health Service Research & Development |
| NICE | National Institute of Clinical Excellence |
| NIST | National Institute of Standards and Technology |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PLR | Powder liquid ratio |
| PLS | Polylysine |
| PPGDMA | Polypropylene Glycol Dimethacrylate diluent monomer |
| QA | Quality Assurance |
| QC | Quality Control |
| RMGIC | Resin Modified Glass Ionomer Cement |
| RT | Room Temperature |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SEM | Scanning Electron Microscopy |
| SOP | Standard Operating Procedure |
| UADE | Unanticipated Adverse Device Effect |
| UDMA | Urethane Dimethacrylate base monomer |
| UK | United Kingdom |
| USADE | Unanticipated Serious Adverse Device Effect |
| UV | Ultraviolet spectroscopy |
| XRD | Xray Diffraction |

# 

# A.1 Overall Synopsis of Clinical Investigation

|  |  |
| --- | --- |
| **Title:** | SMART composite (Self-bonding Material for Atraumatic Restorative Treatment) restoration of children’s primary molar teeth after minimal caries removal: Class IIa device in a single site, single arm study. |
| **Short title:** | SMART filling for caries in primary teeth |
| **Device:** | SMART filling material |
| **Objectives:** | Primary  Stage 1 (Proof of concept)   * Confirm no unexpected adverse events   Stage 2   * Assess percentage restoration failure following 6 months placement of SMART composite on minimally prepared cavities in children’s teeth.   Secondary   * Patient acceptability |
| **Type of Investigation:** | Clinical Investigation of a non CE marked product.  Class IIa,  First in Man – Open label, single site investigation |
| **Investigation design and methods** | Stage 1 – Proof of Concept – 1 month study. Children taking part will be due to have their primary teeth extracted as per standard care. A test filling will be placed in the tooth that is due to be extracted for 1 month. Children routinely wait 1 month between being first seen and tooth extraction and have a temporary restoration during this time. Children will be followed up for any unexpected or adverse events or reactions during this time period.  Stage 2 - 6 month assessment  A new group of children will be assessed in a 6 month study once proof of concept has been established. Children taking part will have decayed primary molar teeth requiring a filling and will be between the ages of 6 and 12 years. Each child will receive a single test filling placed in a randomly selected, caries affected tooth. After six months, the fillings will be clinically assessed to confirm if they are still in place and intact. The children will be checked at 3 months and 6 months for any unexpected or adverse events or reactions. |
| **Investigation duration per participant:** | Stage 1 - 1 month  Stage 2 - 6 months |
| **Estimated total Investigation duration:** | Stage 1  Total 4 months (2 months recruitment and placement, 1 month trial follow-up duration, 1 months IDMC review)  Stage 2  Total 12 months (4 months recruitment and placement, 6 months trial follow-up duration, 2 months analysis, write up and IDMC review) |
| **Planned Investigation sites:** | Eastman Dental Hospital |
| **Total number of participants planned:** | Stage 1  7  Stage 2  59 |
| **Main inclusion/exclusion criteria:** | **Stage 1**  Inclusion   * Children 6 to 12 years of age * One primary molar with a carious cavity affecting one or more surfaces (International Caries Detection and Assessment System (ICDAS) score 4,5) that requires temporary dressing whilst awaiting extraction. * Subject willing to sit in the dental chair and cooperate with clinicians on planned protocol treatment   Exclusion   * Unable to give assent/consent * Non-carious anomaly of structure such as amelogenesis imperfecta * Patients with significant pain and/or infection who require an urgent management (assessed by standard clinical investigations) * Teeth with non-vital exposed pulps with draining pus (as per standard care) * Methacrylate allergy   **Stage 2**  Inclusion   * Children 6 to 12 years of age * One primary molar with a two surface carious cavity (occlusal and proximal surface) ICDAS score 4,5 that requires restoration * Subject willing to sit in the dental chair and cooperate with clinicians on planned protocol treatment   Exclusion   * Unable to give assent/consent * Non-carious anomaly of structure such as amelogenesis imperfecta. * Subject **NOT** willing to sit in the dental chair and cooperate with clinicians on planned protocol treatment * Methacrylate allergy |
| **Statistical methodology and analysis:** | Stage 1 is a proof of concept study.  Stage 2 is an efficacy study looking at failure rates. Stage 1 uses a small sample (7) to check for common adverse events (rate ≥ 0.1). Stage 2 uses a larger sample (59) which will check for failure (rate ≥ 0.01). Levels of failure occurring in Stage 2 will provide population estimates with 95% confidence intervals for comparison with known levels of failure (primarily material drop out) for standard treatment (amalgam filling) within 6 months after placement. At Stage 2 there will be a check-up at 3 months at which the stopping rule will be to stop the trial if upper limit of 95% confidence interval is ≥ 0.20. |

# A.2 Background and Rationale

1. **Dental decay in children – effects, incidence and cost**

Dental decay is one of the most common human diseases and affects 60-90% of school children across the World (WHO, 2012). It is caused by bacteria producing acid that dissolves the tooth structure (enamel and underlying dentine) which, if not halted, can lead to the tooth pulp becoming infected, causing pain, loss of tooth vitality and dental abscess formation. In children, this affects sleeping, eating, general health and well-being. Additionally, infected primary teeth (milk teeth) can damage the underlying adult teeth. Ultimately, these teeth may need to be surgically extracted, but early extraction of decayed primary teeth may lead to abnormalities in tooth alignment (Faculty of Dental Surgery, 2015).

In 2015, 25% of 5 year olds in England had teeth affected by dental decay with each of these children having on average 3 affected teeth. Only 12% of these damaged teeth, however, were filled (National Dental Epidemiological Programme for England, 2015). Consequently, in England, dental decay is the most common reason for a young child to be admitted to hospital in order for the infected teeth to be surgically removed under general anesthesia. The number admitted increased by 14% between 2010-11 and 2013-14 (Faculty of Dental Surgery, 2015). The cost of the 40,970 extractions of multiple teeth in children under 18 carried out in the 2014-2015 period was £35 million (Local Government Association, 2016) but the additional hidden cost of sleepless nights, days off school etc. is unknown. If the affected teeth had been filled successfully at an earlier stage by a general dentist in primary care then general anesthetic would be avoided, reducing risk to patient whilst saving the NHS millions of pounds.

1. **Dental fillings for children.**

When dental decay is diagnosed before the pulp is infected, standard treatment consists of mechanical removal of the diseased hard dental tissues (via drilling) followed by replacement of the lost tissues with a restorative filling material (eg “silver” amalgam, or “white” composite). The decay process in teeth can be halted if diseased tissue is removed and replaced with a filling that effectively seals the cavity. There is evidence that filled primary teeth in children are more than twice as likely to be retained and remain infection-free when compared to unfilled teeth (Stephenson et al, 2010). Unfortunately, restoring teeth in young children is difficult and current materials used are not ideal.

**Amalgam and the Minamata agreement**

The most commonly used restorative material (amalgam) has some advantages - for example it is antibacterial and relatively quick to apply. Amalgam restorations, however, have poor aesthetics and require significant dental tissue removal to ensure retention as this restorative material does not bond to the tooth. Instead retention is achieved by making an undercut and enabling the amalgam to set partially underneath remaining tooth structure. Unfortunately, amalgam contains mercury and is therefore being phased out because of the Minamata agreement that commits the World to a gradual phase down of all mercury containing materials. It is anticipated that the NHS will have to stop using dental amalgam in the treatment of deciduous teeth of children under 15 years by 2020 but there is no ‘true alternative’ available at present for larger cavities (British Dental Association, 2016). Consequently, NHS dentistry will face notable financial challenges as the current number of children with untreated dental decay needing dental surgery under general anesthetic is likely to increase.

**Composites and bonding complexity problems**

Dental composites are a commonly used alternative for adults, but they are difficult to apply in children due to the time-consuming multi-step procedure required to gain effective tooth bonding. Proper application of a composite requires local anesthetic, tooth drilling and multiple other steps to ensure retention (e.g. etching, rinsing, drying, primer / adhesive application and composite layering). This requires patient cooperation for an extended period of time (up to 30 minutes). This is often not possible for a young child to cope with, either because of anxiety (22% of five year olds in England have moderate or extreme dental anxiety, HSCIC 2016) or because they are too young. Furthermore, these composite materials contain toxic components that inhibit natural tooth repair mechanisms and may encourage further decay (Walters et al, 2016).

**Glass ionomer cement (GIC) and hybrid restorative ease of application but reduced strength**

Glass ionomer cements (GIC) are an alternative “white filling” material that can bond directly to caries affected tooth structures without the need for drilling or separate adhesion promoting steps. Instead only surface highly infected tooth structure is removed using a procedure known as Atraumatic Restorative Treatment (ART). Modern dentistry aims to increase treatment procedures such as ART that maintain more of the original tooth structure and encourage tooth self-repair mechanisms. GICs, however, have poor physical properties when compared to the original tooth structure, amalgam and composites (Schwendicke, Gostemeyer et al., 2016). Consequently, they have high failure rates in larger cavities (Hilgert et al, 2014). To address this, over the past 20 years a large number of hybrid materials that contain components of GICs, composites and composite adhesives have been developed. All these hybrids, however, still have either insufficient strength for large cavities and / or need complex procedures to gain effective tooth bonding and sealing. Possibly the most successful hybrids have been the resin modified glass ionomer cements (RMGIC). But, in addition to having only moderate strength, RMGICs generally contain a small methacrylate monomer which, due to its small size, is volatile and can cause high toxicity to human cells and allergic reactions (Sidhu and Nicholson, 2016).

1. **Current material failure rates**

Restoration failure rates are dependent upon many factors including restoration size, position in the tooth and mouth, restorative material, clinician’s expertise, cavity preparation, disease progress / recurrence and patient age and oral hygiene. Analysis of data from a multi-center study of ~530 large multi-surface restorations in primary molar teeth found early percentage failure rates for non-bonded amalgam and GIC were both >20% per year. By 3 years, amalgam and GIC average failures reached 35 and 44% respectively with the main clinical observation being partial or complete loss of the restoration (Hilgert et al, 2014). In an earlier study with ~700 multi-surface molar restorations, average failures after 3 years were 52% for GICs. This reduced to 35% with stronger RMGICs but these materials failed badly (50% in 3 years) when bonded to an incisor (Qvist et al 2004). A further review of multiple studies concluded that RMGIC should only be used in small to moderate sized molar cavities (Chadwick and Evans, 2007). Conversely, with strong bonded composite restorations in adult teeth, analysis of multiple studies shows failures can be less than 20% after 10 years in molars (Opdam et al 2014). As restorations in primary teeth may require a lifetime of up to 10 years, a strong self-bonding composite that could be more reproducibly and simply applied using a minimally invasive ART type approach would be of considerable benefit.

1. **SMART new self-bonding composite material**

Details of the components in a new SMART Self-bonding composite for Atraumatic Restorative Treatment to be used in the clinical trial are provided below. In unpublished laboratory studies, this SMART composite has been shown to be able to bond and seal both sound and carious tooth structures without need of either tooth etching or application of conventional primers and adhesives. Tubules in dentine allow passage of bacteria, water and dissolved components (eg acid or nutrients for bacteria) from the surface enamel down to the pulp. When attacked by acid the pulp encourages sealing of these tubules by precipitation of apatite minerals but this tooth self-defence process takes time. Sealing of the cavity and dentine tubules by the restorative material helps prevent disease continuation whilst this natural repair process occurs. Laboratory studies in extracted teeth has shown this sealing is more effective with the SMART composite than observed with commercial conventional composites employed using the standard complex bonding and dentine sealing procedures. Furthermore, the SMART composite can self-repair if fractured and reseal the tooth / restoration interface if it becomes damaged. It also outperformed an RMGIC and a recently marketed hybrid material bonding / cavity sealing ability (*Summary of all bench testing and pre-clinical testing conducted*).

As is generally the case with new Class IIa dental composites that pass ISO standard tests, the final SMART composite formulation has not been pre-tested in animals. It has, however, been shown to pass cell compatibility tests required by ISO 7405:2008 and a risk assessment has been performed according to ISO 14971:2012 by a multidisciplinary team with an experienced regulatory advisor. Furthermore, biocompatibility of individual composite components has been demonstrated through extensive literature review and cell compatibility testing (Walters et al., 2016). Likelihood of restoration success can be predicted through comparison with a wide range of other restorative materials using multiple standard and in-house developed laboratory methods. Additionally, a simpler procedure with fewer steps will provide an inherently less risk prone method of tooth restoration. As the patient group, however, is children a staged approach is employed in this proposed clinical study using in the first instance teeth destined for early extraction to further reduce risk.

# A.6 Objectives and hypotheses of the clinical investigation

## *A6.1 Hypotheses*

The Clinical Investigation hypothesis is that the composite is safe, will seal cavities and have failure rates comparable or less than observed with amalgam in large primary molar cavities.

## *A6.2 Primary Objective*

Stage 1 (proof of concept)

* Confirm no unexpected adverse events

Stage 2

* Assess percentage restoration failure following 6 months placement of SMART composite on minimally prepared cavities in children’s teeth.



## *A6.3 Secondary Objective(s)*

Secondary

* Patient acceptability

# A.7 Design of the clinical investigation

## *A.7.1 General*

Stage 1 – Proof of Concept – 1 month study. Children taking part will be due to have their primary teeth extracted as per standard care. A test filling will be placed in the tooth that is due to be extracted for 1 month. Children routinely wait 1 month between being first seen and tooth extraction. Children will be followed up for any unexpected or adverse events or reactions during this time period.

Stage 2 - 6 month assessment

A new group of children will be assessed in a 6 month study once proof of concept has been established. Children taking part will have decayed primary molar teeth requiring a filling and will be between the ages of 6 and 12 years. Each child will receive a single test filling placed in a randomly selected, caries affected tooth. After six months the fillings will be clinically assessed to confirm if they are still in place and intact. The children will be checked at 3 months and 6 months for any unexpected or adverse events or reactions.

## *A.7.2 Investigational device and comparators*

SMART composite (Self-bonding Material for Atraumatic Restorative Treatment)

No comparator

## *A.7.3 Subjects*

**Stage 1**

Inclusion

* Children 6 to 12 years of age
* One primary molar with a carious cavity affecting one or more surfaces (International Caries Detection and Assessment System (ICDAS) score 4,5) that requires temporary dressing whilst awaiting extraction.
* Subject willing to sit in the dental chair and cooperate with clinicians on planned protocol treatment

Exclusion

* Unable to give assent/consent
* Non-carious anomaly of structure such as amelogenesis imperfecta (this data will be in the patient records).
* Patients with significant pain and/or infection who require an urgent management (assessed by standard clinical investigations)
* Teeth with non-vital exposed pulps with draining pus (as per standard care)
* Methacrylate allergy

**Stage 2**

Inclusion

* Children 6 to 12 years of age
* One primary molar with a two surface carious cavity (occlusal and proximal surface) ICDAS score 4,5 that requires restoration
* Subject willing to sit in the dental chair and cooperate with clinicians on planned protocol treatment

Exclusion

* Unable to give assent/consent
* Non-carious anomaly of structure such as amelogenesis imperfecta.
* Subject **NOT** willing to sit in the dental chair and cooperate with clinicians on planned protocol treatment
* Methacrylate allergy

***Criteria and procedures for subject withdrawal or discontinuation***

Participants will be withdrawn if;

* They do not attend for the final visit
* The participant decides they no longer wish to continue and withdraw consent
* Recommended by the investigator

Participants have the right to withdraw from the study at any time for any reason. However, should the patient or their parents wish to withdraw the patient from the study they will be informed that the composite will not be removed (unless deemed clinically required). The investigator also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE’s, or other clinically significant reasons.

Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. We do not intend to replace the filling material if patients withdraw as the risks of repeating the restoration outweigh leaving it in a primary tooth that will ultimately exfoliate. Patient data will not be used.

Patients who withdraw will not be replaced unless withdrawal is prior to placement of the composite as later stage withdrawals are accounted for in the statistics.

***Point of enrolment.***

Enrollment into the study occurs when the patient has completed the consent process, confirmed as suitable for inclusion and attends for SMART composite placement.

***Total expected duration of the clinical investigation.***

Stage 1 will be 4 months

Stage 2 will be 12 months

*Subject Eligibility*

Once written informed consent has been obtained, the Case Report Form will be completed to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed consent form and completed inclusion/exclusion criteria retained by the Chief Investigator. The subject will not be advanced any further into this clinical investigation.

***Subject Identification***

When a subject is identified and considered eligible for entry into this clinical investigation, the subject will be allocated the next available investigation number (subject ID number).

## *A7.4 Recruitment*

Participant recruitment at the designated site will only commence when the trial has been initiated by the Sponsor (or its delegated representative), and issued with the ‘Open to Recruitment’ letter.

Recruitment methods

Stage 1

Potential participants will already be attending the Eastman Dental Hospital. They will be given information as part of their normal care and then asked if they would like to take part.

Stage 2

Potential participants will already be attending the Eastman Dental Hospital. At the patient’s routine appointment, the CI will discuss the trial with the patient/guardian and provide a copy of the patient information sheet. The patients/guardians will be given ample time should they wish to participate (at least 24 hours).

## *A7.5 Registration Procedures*

Participant registration will be undertaken centrally by the coordinating trial team. When a subject is identified and considered eligible for entry into this clinical investigation, the subject will be allocated the next available investigation number (subject ID number).

For subjects enrolled, this number will consist of 01 for the first subject, 02 for the second subject and so on. This number will be the unique identifier of the subject and written on each page of the paper Case Report Form booklet and all other documentation relating to that subject.

Each subject that is enrolled into the study will have their study participation recorded and details of the device recorded in their hospital notes, a copy of their signed consent form and patient information sheet should also be placed on his/her hospitals notes to identify the subject as participating in a Clinical Investigation.

Participants are considered to be enrolled into the trial following consent.

## *A.7.6 Informed Consent Process*

The CI, or a person delegated by the Investigator will obtain written informed consent from each subject prior to participation in the investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study to both parent and child participant.

The person taking consent will be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI on the delegation log.

Adequate time will be given for consideration by the participant and their parent/guardian before taking part. The CI will record when the patient information sheet (PIS) has been given to the family which will be at least 24 hours before the study enrollment. It will be recorded in the medical notes when the participant information sheet (PIS) has been given to the participant.

The Investigator or designee will explain the patients are under no obligation to enter the Investigation and can withdraw at any time during the Investigation, without having to give a reason.

Consent will denote enrolment into Investigation. A copy of the signed Informed Consent Document will be given to the participant and their parent/guardian. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and participants will be re-consented as appropriate.

# A.8 Procedures

The Study Schedule (Appendix A), and Section A.9 illustrate the activities and timings associated with the clinical study. All investigations will be part of routine/standard care. Where more than one tooth in a patient is eligible for inclusion, the tooth for inclusion in the study will be selected randomly using a sealed envelope technique (first quadrant will be selected then the tooth i.e. first or second primary molar)

# Schedule of assessments and interventions by visit

**(see also Appendix A)**

Stage 1 – Proof of Concept

|  |
| --- |
| **Visit 1 Screening** |
| Dental and medical history |
| Clinical oro-facial examination |
| Inclusion/exclusion criteria assessment |
| Invitation to take part |
|  |
| **Visit 2 Intervention** |
| Consent for study |
| Record demographic data |
| Identify all teeth with cavities requiring temporary restoration before extraction. |
| Ensure objectivity (avoid experimenter bias) by selecting experimental tooth at random from identified teeth using systematic random selection process |
| Place experimental composite (Device) |
| Complete questionnaire (acceptability) |
|  |
| **Visit 3 Extraction** |
| Clinical oro-facial examination and take history regarding any adverse events |
| Removal of tooth |

**Stage 2**

|  |
| --- |
| **Visit 1 Screening** |
| Dental and medical history |
| Clinical oro-facial examination |
| Inclusion/exclusion criteria assessment |
| Invitation to take part |
|  |
| **Visit 2 Intervention** |
| Consent for study |
| Record demographic data |
| Identify all teeth having well defined multi-surface cavities and needing restorations. |
| Ensure objectivity (avoid experimenter bias) by selecting experimental tooth at random from identified teeth using systematic random selection process |
| Place experimental composite (Device) |
| Complete questionnaire (acceptability) |
| **Phone interview at 3 months to check for any adverse events** |
| **Visit 3 - 6 month review** |
| Dental and medical history |
| Clinical oro-facial examination |
| Clinical oro-facial examination and take history regarding any adverse events |

## *A9.0* *Laboratory Assessments and Procedures*

No laboratory tests will be undertaken as part of the clinical trial.

# A.10 Device accountability

Compules will be delivered by the Eastman Dental Hospital by Davis Schottlander & Davis Ltd, device order/receipt forms will be completed. Access to the compules will be closely monitored and controlled according to the rules and regulations set out in ISO 14155:2011. The physical location of the compules shall be documented. The compules will be kept in a lockable sealed fridge on the Paediatric Dentistry Department.

For the purpose of device accountability records kept about the compules shall include

1. Date of receipt
2. Identification of each compule (LOT number, dependent on batch of compule)
3. The expiry date
4. The date of use
5. Subject identification
6. Date of return of unused, expired or composite not fit for use, if applicable

This is a clinical Investigation of a non CE marked device. Device accountability logs will be maintained in the Investigator Site File. Unused compules will be kept at the Eastman Dental Institute and used for *in vitro* investigations.

# A.11 Monitoring Plan

Paper Case Report Forms (CRFs) will be completed by the investigator and/or his/her delegates within 5 working days of the study visit. All data from the examinations and investigations listed in section 9.0 will be transferred to the CRF.

The sponsor will perform interim monitoring visits at least every 4-6 weeks during the study. The first interim monitoring visit shall occur no more than 30 days following the first patient intervention. The site will allow access to the study patients’ records for source verification, in line with the monitoring plan. The sponsor will schedule interim monitoring visits with advance notice and confirm the scheduling of the visit with the study site. The sponsor representative should meet with the investigator at each monitoring visit.

The investigator(s)/ institution(s) will permit Investigation-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Investigation participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

The sponsor representative shall perform the following activities at each monitoring visit;

* Source verification in line with the monitoring plan
* Essential document review
* Deviation review
* Adverse event review

At the conclusion of the monitoring visit, the sponsor representative shall write a monitoring report detailing the activities performed during the visit with recommendations for action items and study site action. A follow-up letter to the study site detailing these recommendations and actions will be sent to the investigator.

### Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The CRFs will not bear the subject’s name or other personal identifiable data. The subject’s initials, date of birth and Investigation identification number, will be used for identification. Subjects will be assigned an Investigation identification number by the study site sequentially starting with 01 upon enrolment into the study. The study site will maintain a master Subject Identification Log.

### Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential Investigation documents as per their Trust policy. All essential documents will be archived for at least 10 years after completion of Investigation. Destruction of essential documents will require authorisation from the Sponsor.

# A.12 Statistical Considerations

The study design is a single arm ‘first in humans’ study focussing on identification of adverse events in the first part and estimating their rates in the population with adequate precision. The second stage will investigate failure rates. Stage 1 uses a small sample to check for common adverse events (rate ≥ 0.1). Stage 2 uses a larger sample which will check for failure (rate ≥ 0.01). Rates of failure occurring in Stage 2 will provide population estimates with 95% confidence intervals for comparison with known rates for failure for standard treatment (amalgam filling).

Stage 1 sample size n=7 (allowing for 1 drop out) provides a 0.45 probability of revealing at least one incidence of an adverse event that has a 1 in 10 occurrence rate in the population, and that Stage 2 with a sample size of 59 (allowing for 9 dropouts) has at least a 0.39 probability of revealing at least one incidence of an adverse event that has a 1 in 100 occurrence rate in the population.

1. the level of significance and the power of the clinical investigation,

Stage 2; the failure rate of the standard treatment (amalgam) is approximately 10% over this time period. This rate (0.1) would provide a 95% confidence interval of (0.033 to 0.218).

1. expected drop-out rates,

The expected drop out rates are 15% hence initial sample sizes will be 7 for Stage 1 and 59 for Stage 2.

1. pass/fail criteria to be applied to the results of the clinical investigation,

Stage 1 – any adverse event.

Stage 2 – greater than 20% rate of adverse events.

1. the provision for an interim analysis, where applicable,

At Stage 2 there will be telephone contact at 3 months.

1. criteria for the termination of the clinical investigation on statistical grounds,

At Stage 2 there will be telephone contact at 3 months at which the stopping rule will be to stop trial if upper limit of 95% confidence interval is ≥ 0.20.

1. procedures for reporting any deviation(s) from the original statistical plan,

All deviations will be notified to the Sponsor and Statistician prior to implementation.

1. procedures that take into account all the data,

Contact will be attempted for all patients not attending follow up.

1. the treatment of missing, unused or spurious data, including drop-outs and withdrawals,

Descriptive analyses of drop outs and withdrawals.

Data Management procedures will be detailed in trial specific Data Management Standard Operating Procedure.

The handling and entry of all data on the paper CRFs will be the responsibility of CI. All data will be recorded in the patients’ medical notes and then transcribed to the paper CRF, please refer to section 13.

Descriptive data analysis will be performed for both primary and secondary objective for Stages 1 and 2 of the trial.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling. The sponsor will have full access to data to enable quality checks.

# A13 Procedures for data review, database cleaning, and issuing and resolving data queries.

Data entered on the CRFs will be source verified by a sponsor representative, in line with the monitoring plan, who is trained on the CIP and who has current GCP training. Data Clarification Forms (DCF) will be issued to the Investigator should a discrepancy be found between the source and CRF. The Investigator will be required to verify and correct all errors or provide an explanation for the discrepant data. Sponsor representatives will re-verify the corrected data and mark the clarification as resolved at the next monitoring visit.

## *A13.1 Data retention*

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential Investigation documents as per their trust policy. All essential documents will be archived for at least 20 years after completion of Investigation. Destruction of essential documents will require authorisation from the Sponsor.

## *A13.2 Clinical quality assurance*

The CI (Paul Ashley) and overall project manager (Anne Young) will meet monthly to discuss any issues with data quality and laboratory results. Any concerns will be discussed with the Sponsor.

## *A13.3 Completion of Case Report Forms (CRF)*

The CI will be responsible for the timing, accuracy and completeness of a CRF for each individual subject. All entries are to be made in black ink and are to be legible. All corrections made are to be completed by placing a single line through the incorrect data and the individual making the correction must initial and date the correction. Typing correction fluid must not be used. The personal data recorded on all documents will be regarded as confidential.

The CI must record the subject’s participation in this clinical investigation in the subject’s hospital notes. In addition, the CI investigator must keep a separate list of all subjects entered into the clinical investigation showing each subject’s name, date of birth and assigned subject number (for identification purposes). A Subject Identification Log will also be provided in the Investigation Site File to record the subject’s initials and assigned subject number.

All data will be handled in accordance with the UK Data Protection Act 1998.

The CRFs will not bear the subject’s name or other personal identifiable data. The subject’s initials, date of birth and trial identification number, will be used for identification.

## *A13.4 Review and Return of Completed Documentation*

The CI investigator will make the original Case Report Forms available to the Sponsor’s designated monitor at each visit. At the conclusion of the clinical investigation, completed Case Report Forms will be signed by the CI, collected (the original left with the CI) and a copy returned to the Sponsor.

## *A13.5 Retention of Documentation*

The CI will retain all copies of the records for a period of 20 years from the discontinuation of the clinical investigation. In all cases, the CI must contact the Sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are signed Clinical Investigation Plan, copies of the CRFs, signed consent forms, ethics committee approval letters, product accountability records, correspondence concerning the clinical and any other documents to identify the subjects.

In addition, if the CI moves/retires, etc., University College London will be provided with the name and address of the person who will look after and be responsible for the clinical investigation related records.

## *A13.7 Training*

During the initiation of the investigation site, the sponsor will ensure the investigators and the site study staff are trained on the device. The investigator is then responsible for ensuring that the investigation staff uses the device in the same way. All training will be documented in a Site Training Log.

The monitor will also ensure that the investigator and investigation site team have received and understood the requirements and content of:

\* CIP (Clinical Investigation Plan)

\* IB (Investigators Brochure)

\* The informed consent forms

\* CRFs (Case Report Forms)

\* IFUs (Instructions For Use)

\* All written clinical investigation agreements as appropriate

# A.14 Amendments to the CIP

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the Investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff has been trained. This process does not affect the individual clinician’s responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

# A.15 Deviations from clinical investigation plan

A deviation is considered a departure from the conditions and principles of GCP in connection with that Investigation; or the CIP relating to that Investigation, as amended from time to time.

The Investigator shall not deviate from this CIP except in situations that affect the subject’s rights, safety and well-being, or the scientific integrity of the clinical investigation.

## A.15.1 Procedures for recording, reporting and analysing CIP deviations

If possible, prior approval from the sponsor and REC, if appropriate, shall be obtained by the investigator. **All spontaneous CIP deviations shall be recorded and reported to the sponsor** as agreed. A deviation log shall be maintained by the study site. Deviations shall be reported to the REC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

**Notification requirements and time frames.**

Requests for deviations by the investigator will be responded to within 24 hours of receipt.

**Corrective and preventive actions:.**

Refer to the Monitoring Plan (as applicable) for corrective and preventative actions

## A.15.2 Procedure for reporting any CIP deviations

Any deviation from the protocol that has not been previously approved by the sponsor (JRO at University College London), must be reported to the sponsor within 2 working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified during routine monitoring visits will be reported to the sponsor (JRO, University College London) within 24 hours of being identified.

**A.16 Statements of compliance**

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable device and UK regulations.

The clinical investigation shall not commence recruitment until all REC, regulatory (if applicable) and local (NHS permission) is received. All additional requirements imposed by the REC or regulatory authority will be followed.

# A.17 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor’s Insurers, via the Sponsor’s office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

# A.18 Adverse events, adverse device effects and device deficiencies

## Definitions

|  |  |
| --- | --- |
| **Term** | Definition |
| **Adverse Event (AE)** | Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.  **Note 1:** This definition includes events related to the investigational medical device or the comparator  **Note 2:** This definition includes events related to the procedures involved  **Note 3:** For users or other persons, this definition is restricted to events related to investigational medical devices |
| **Adverse Device Effect (ADE)** | Adverse Event related to the use of an investigational device.  **Note 1:** This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device  **Note 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device |
| **Serious Adverse Event (SAE)** | Any adverse event that:   * Led to death, * Led to serious deterioration in the health of the subject, that either resulted in * a life-threatening illness or injury, or * a permanent impairment of a body structure or a body function, or * in-patient or prolonged hospitialisation, or * medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, * Led to foetal distress, foetal death or a congenital anomaly or birth defect |

|  |  |
| --- | --- |
| **Serious Adverse Device Effect (SADE)** | An ADE that has resulted in any of the consequences characteristic of an SAE |
| **Unanticipated Serious Adverse Device Effect (USADE)** | An SADE, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report. |
| **Device Deficiency (DD)** | Inadequately of a medical device with respect to its identity, quality, durability, reliability, safety or performance.  **Note 1:** this includes malfunctions, use errors, and inadequate labeling |

An adverse event does not include:

Medical or surgical procedures; the condition that leads to the procedure is an adverse event.

Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity.

Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);

The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject’s condition.

Expected post-operative course (see section x)

## Reporting requirements and timelines

AEs and ADEs are not considered reportable.

|  |  |  |  |
| --- | --- | --- | --- |
| Term | Reporter | Reported to | Reporting Timeline from awareness of the event |
| Adverse Event (AE) | Investigator | Sponsor | As agreed with sponsor. CI to record fully all AEs. |
| Adverse Device Effect (ADE) | Investigator | Sponsor/Manufacturer | As agreed with sponsor. CI to record fully all ADEs. |

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of DIRECTIVES 90/385/EEC AND 93/42/EEC respectively.

|  |  |  |  |
| --- | --- | --- | --- |
| Term | Reporter | Reported to | Reporting Timeline from awareness of the event |
| Serious Adverse Event (SAE)\*\*/ Serious Adverse Device Effect (SADE) | Investigator | Sponsor | Immediately, but no more than 3 calendar days after becoming aware of the event |
| CI | MHRA [aic@mhra.gsi.gov.uk](mailto:aic@mhra.gsi.gov.uk) | Immediately, but not later than 2\* calendar days after awareness  \*For SAEs which indicate an imminent risk of death, serious injury, or serious illness and  that require prompt remedial action for other patients/subjects, users or other persons  All other events immediately but not later than 7 calendar days following date of awareness. |
| CI | REC | N/A |
| Unanticipated Serious Adverse Device Effect (USADE) | Investigator | Sponsor | Immediately, but no more than 3 calendar days after becoming aware of the event |
| CI | MHRA | Immediately, but not later than 2\* calendar days after awareness  \*For SAEs which indicate an imminent risk of death, serious injury, or serious illness and  that require prompt remedial action for other patients/subjects, users or other persons.  All other events immediately but not later than 7 calendar days following date of awareness. |
| CI | REC | Within 15 days of the chief investigator becoming aware of the event.  Only reports of related and unexpected Serious Adverse Events (SAEs) should be submitted to the REC. |

|  |  |  |  |
| --- | --- | --- | --- |
| Term | Reporter | Reported to | Reporting Timeline from awareness of the event |
| Device Deficiency (DD) | Investigator | Sponsor | Immediately, no more than 24 hours of becoming aware of the event |
| CI | MHRA | 7 calendar days  Only reportable if the event may have led to an SAE if;   * suitable action had not taken * intervention had not been made * if circumstances had been less fortunate |
| Urgent Safety Measures | CI | REC | 1. Immediately-By telephone 2. Within 3 days-Notice in writing setting out reasons for the USM and plan for further action |

\*\* **Note** Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

## Assessments of adverse events

Each adverse event will be assessed for the following criteria:

### Severity

|  |  |
| --- | --- |
| Category | Definition |
| Mild | The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort |
| Moderate | The adverse event interferes with some aspects of the subjects routine, or requires intervention, but is not damaging to health; it causes moderate discomfort |
| Severe | The adverse event results in alteration, discomfort or disability which is clearly damaging to health  Note: A severity rating of severe does not necessarily categorise the event as an SAE. |

### Seriousness

Seriousness as defined for an SAE in section a) above.

### Causality

The assessment of relationship of adverse events to the study procedure and the investigational device will be a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

|  |  |
| --- | --- |
| Category | Definition |
| Yes | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely |
| Possibly | There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after procedure). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant events). |
| No | There is no evidence of any causal relationship. |

### Expectedness

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event that is consistent with the information about the device listed in the Investigator Brochure or clearly defined in this CIP. |
| *Unexpected* | An adverse event that is not consistent with the information about the device listed in the Investigator Brochure |

The reference document to be used to assess expectedness against the intervention is the IB. The CIP will be used as the reference document to assess disease related and/or procedural expected events.

## Procedures for recording and reporting Adverse Events and Device Deficiencies

### Investigator responsibilities:

All adverse events and SAEs will be recorded in the medical records and CRF following consent.

All serious adverse events will need to be reported to the sponsor on a SAE form (using MEDDEV form 2.7/3)

The CI will complete the serious adverse event form and the form will be emailed to the sponsor within 3 working day of his/her becoming aware of the event. The CI will respond to any SAE queries raised by the sponsor as soon as possible.

The Investigator will report to the MHRA and REC (as applicable) all reportable events within the specified timeframes as per section d above.

*Only deaths that are assessed to be caused by the device will be reported to the sponsor. This report will be immediate*

All SAEs and UADEs should be reported to the following;

Fax: 020 3108 2312

e-mail: CTIMPs@ucl.ac.uk

## Reporting of all Adverse Events and Device Deficiencies: Investigator and Sponsor responsibilities

Investigator responsibilities shall be as per section d). The sponsor shall keep detailed records of all adverse events and device deficiencies relating to the clinical Investigation, which are reported to them by the Investigation investigators. The sponsor shall ensure that all relevant information about a reportable event, which occurs during the course of this clinical Investigation in the United Kingdom, is reported as soon as possible to the MHRA, and the relevant ethics committees per their reporting requirements and according to the timelines in section d. Any additional relevant information should be sent within the same time frame as the initial report. The CI is responsible for informing the appropriate regulatory authorities, ethics committees and other investigators of any reportable events that have occurred with the study device in any clinical investigation according to the guidelines set forth by either the REC of record or regulatory authority in the country where the clinical investigation is taking place.

## Progress reports

Progress reports will be submitted to the REC as per the REC requirements. The CI will prepare the annual progress reports.

## Foreseeable adverse events and anticipated adverse device effects

### List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment.

**Loss of filling material.**

For similar materials 1 in 10 occurrence is reported. However, as this material has improved properties, incidents should be less frequent. If this does occur;

Stage 1

The filling will not be replaced due to the relatively short interval of time between restoration placement and tooth extraction.

Stage 2

The patient will have another scheduled appointment to have the filling replaced.

**Allergic reaction**

Allergies to methacrylate are uncommon. They are most likely to cause contact dermatitis but this has only been reported with frequent contact with uncured monomers. In this study risks are extremely low and if they do occur likely to only cause mild irritation. If an allergic reaction is detected the filling can be removed.

# A.19 Oversight Committees

**Trial Management Group (TMG)**

The TMG will include the Chief Investigator, and experts from relevant specialties.  The TMG will be responsible for overseeing the trial.  The group will meet at least twice per year and all members will sign a TMG charter.  The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA.

**Trial Steering Committee (TSC)**

The role of the TSC is to provide overall supervision of the trial.  The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary.  The TSC acts on behalf of the funder(s) and the Sponsor. All Trial Steering Committee Members will sign a TSC charter.

**Independent Data Monitoring Committee (IDMC)**

The role of the IDMC is to provide independent advice on data and safety aspects of the trial.  Meetings of the Committee will be held bi-annually to review the safety data generated by the study or as necessary to address any issues.  The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC. All IDMC members will sign an IDMC charter.

# A.20 Vulnerable population

If applicable include:

a) Description of the vulnerable population.

Children as described previously

b) Description of the specific informed consent process.

The consent process has been described previously (A8) in this document

c) Description of the EC's specific responsibility.

N/A

d) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

Clinical care will not be disrupted by this clinical investigation

# A.21 Suspension or premature termination of the clinical investigation

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the ethics committee concerned or any other relevant authority or committee. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. Subjects will be followed up pas stated in section A8

The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

Both the Sponsor and the CI reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the clinical investigation, the JRO at University College London and the CI will assure that adequate consideration is given to the protection of the subject’s interests.

# A.21 Definition of End of Trial

End of trial is the date the last participants in Stage 2 to have the composite place will have 6 month follow-up appointments.

After trial completion we intend to continue with passive data collection from these patients

**A.22 Publication policy**

The results of this investigation will be offered for publication with a timeline of 6 months from trial completion to submission. All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to UCL publication policy.

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Stage 1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ***Screening*** | ***Baseline a*** | ***Treatment Phase b*** | |
| *Visit #* | *1* | *2* | *3* |
|  | *Day – 1* | *Day-7* | *1 month* |
| *Informed Consent* |  | *x* |  |
| *Medical History/Physical exam* | *x* |  |  |
| *Vital Signs* |  |  |  |
| *Eligibility determination* | *x* |  |  |
| *Device/Treatment* |  | *x* |  |
| *Adverse Events review* |  | *x* | *x* |
| *Concomitant Medication review* |  | *x* |  |
| *Physician’s Withdrawal Checklist* |  |  |  |

Stage 2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ***Screening*** | ***Baseline a*** | ***Treatment Phase b*** | |
| *Visit #* | *1* | *2* | *3* |
|  | *Day – 1* | *Day-7* | *6 month* |
| *Informed Consent* |  | *x* |  |
| *Medical History/Physical exam* | *x* |  |  |
| *Vital Signs* |  |  |  |
| *Eligibility determination* | *x* |  |  |
| *Device/Treatment* |  | *x* |  |
| *Adverse Events review* |  | *x* | *x* |
| *Concomitant Medication review* |  | *x* |  |
| *Physician’s Withdrawal Checklist* |  |  |  |