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| **Full title of trial** | Assessing the acceptability of the Wand computer-controlled local anaesthetic device for paediatric dental patients: A pilot clinical trial |
| **Short title** | Acceptability of the Wand for young dental patients |
| **Version and date of protocol** | Protocol Version 3, 15/07/2020 |
| **Sponsor:** | University College London (UCL) |
| **Sponsor R&D reference**  | 125424 |
| **Funder(s):** | The Cultural Affairs Department at the Libyan Embassy-London  |
|  |  |
| **Intervention:** | The Wand computer-controlled local anaesthetic delivery system |
| **Single site/multi-site:** | Single site |

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| --- | --- |
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Protocol version history

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| --- | --- | --- | --- |
| Version Number | Date | Protocol Update Finalised By (insert name of person):  | Reasons for Update |
| 1 | 02/02/2019 | Rema Elhaj-Husian | Ethics submission |
| 2 | 10/07/2020 | Rema Elhaj-Husian | REC review |
| 3 | 30/10/2020 | Rema Elhaj-Husian | REC review |

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor’s SOPs, and other regulatory requirements as amended.

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| --- | --- | --- |
| **Chief investigator**Prof. Paul Ashley |  | 3/1/20 |
| UCL | Signature | Date |
| **Sponsor** Sponsor representative |   | 06/01/2020 |
| UCL | Signature | Date |
|  |  |  |

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List of abbreviations

|  |  |
| --- | --- |
| AE  | Adverse Event |
| APR  | Annual Progress Report |
| ASA  | American Society of Anaesthesiology |
| CCLAD  | Computer-Controlled Local Anaesthetic Device |
| CI  | Chief Investigator |
| CIRP  | Children’s Intervention Rating Profile |
| CRF  | Case Report Form |
| DATIX  | Web-based incident and risk reporting software |
| EDH  | Eastman Dental Hospital |
| EDI  | Eastman Dental Institute |
| ICF  | Informed Consent Form |
| IPR  | Intellectual Property Rights |
| ISRCTN  | International Standard Randomised Controlled Trial Number |
| LA  | Local Anaesthetic |
| MCDAS  | Modified Child’s Dental Anxiety Scale |
| NHS R&D  | National Health Service Research & Development |
| PI  | Principal Investigator |
| PIS  | Participant Information Sheet |
| PPI  | Public and Patient Involvement |
| PROMs  | Patient Reported Outcome Measures |
| RCT  | Randomised Controlled Trial |
| REC  | Research Ethics Committee |
| SAE  | Serious Adverse Event |
| TMG  | Trial Management Group |
| UCLH  | University College London Hospitals |
| VAS  | Visual Analogue Scale |

Trial personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

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Summary

|  |  |
| --- | --- |
| *Objectives:* | To compare child dental patients’ acceptability of local anaesthetic (LA) delivered by the Wand computer-controlled local anaesthetic delivery system (CCLAD) to LA delivered by the conventional dental syringe.  |
| *Type of trial:* | A parallel unblinded randomised controlled pilot trial.  |
| *Trial design and methods:* | This is a pilot unblinded single-site parallel randomised controlled trial to compare two groups of participants. The intervention group will receive the intervention treatment (dental local anaesthetic LA via the Wand CCLAD system), and the control group will receive the control treatment (dental local anaesthetic LA via the conventional dental syringe).The two groups will be compared in terms of their acceptability of the LA delivered by the two methods.Eligible participants will be recruited and randomised to receive either LA delivery method. The acceptability of these methods will be assessed using anxiety scales and acceptability rating profiles.  |
| *Trial duration per participant:* | The trial is a one-off procedure for each participant. The consent of participants and their parents/legal guardians will be obtained on the day of the trial at the trial site just before their randomisation. Every participant will then complete an anxiety scale and a prospective acceptability rating profile before receiving the treatment. Immediately after receiving the LA, each participant will complete an acceptability visual analogue scale, then after completion of the treatment, each participant will complete another anxiety scale, dental injection fear profile, and a retrospective acceptability rating profile. By achieving this stage, the trial should be completed for each participant. The duration will be the normal treatment time added to the time every participant requires to complete the rating scales, which with the consent/assent process (including explaining the study) is estimated to take approximately 60 minutes in total. |
| *Estimated total trial duration:* | Approximately 2 months |
| *Planned trial sites:* | Single-site: Eastman Dental Hospital  |
| *Total number of participants planned:* | 30 |
| *Inclusion criteria* | * Paediatric patients aged 10-16 yrs.
* No previous experience of having LA delivered by the Wand.
* Requiring dental treatment under LA.
* Good general health (American Society of Anaesthesiology ASA classification I & II).
* Able to understand English sufficiently to complete scales/rating profiles appropriately
* Patients and guardians willing to give informed assent/consent to participate in the study.
* Co-operative, with no indication of conscious sedation or treatment under general anaesthesia.
 |
| *Exclusion criteria* | * Aged below 10 or over 16 years old.
* Children unable to understand English sufficiently.
* Requiring treatment under conscious sedation or general anaesthesia
* Children with ASA class III or over.
* Patients who have previously received dental anaesthesia using the Wand.
* Unwilling to give consent.
 |
| *Statistical methodology and analysis:* | In the absence of similar published trials, pilot studies are often used to determine the information required to conduct a sample size calculation. As there is no publicly available information on similar trials, it is therefore not reasonable to conduct a sample size calculation in this case. It is anticipated that this pilot trial will, however, yield information that will help with sample size calculations for future similar studies.The number of participants will be decided by considering the realistic number of children that could be recruited within the timeframe allocated to the pilot study. Data will be summarised and analysed descriptively, using tables and graphs as required. As the sample size is not large, the categories compared need will be kept to the minimum, to avoid negligible numbers in each category. |

# Background and rationale

Dental anxiety is a common phenomenon, particularly among children and young adults (Locker et al., 2001, 1999), which forms a burden on dental and general health due to deferring, cancelling, or not attending dental appointments (Milgrom, Vignehsa, & Weinstein, 1992; Rãducanu et al., 2009). It was defined in its most basic form as “a general state in which the individual experiences a level of apprehension and is prepared for something negative to happen” (Porritt et al., 2012). The most common evoking stimuli of dental anxiety are dental needles and drills (Taani et al., 2005). Dental needles (conventional syringes) are used to inject the local anaesthetic (LA) to a specific site of the oral cavity where the dental treatment is required, as an essential measure to provide painless dental treatment.

One recent advancement in reducing the discomfort associated with the delivery of LA is the computer-controlled local anaesthetic device (CCLAD). The first CCLAD, named the ‘Wand®’ (a proprietary registered trademark, hereinafter referred to as ‘Wand’), was developed by Milestone Scientific™ and introduced in 1997. As per the American Dental Association, “the Wand local anaesthetic delivery system is accepted as a device that has been shown to safely and effectively deliver anaesthetic solution when used by an appropriately qualified professional” (Lieberman, 1999). It works by controlling and stabilising the flow rate of the injection and was introduced as a pain-free LA injection to eliminate triggering factors of the pain-anxiety vicious cycle. As the pressure produced by the quick and inconsistent injection of local anaesthesia (LA) is one of the causes of pain, the LA injection manner of the Wand potentially provides a significantly improved injection experience (Gibson et al., 2000). It has been in utilisation since 1997, and research has showed its effectiveness in delivering the LA with less discomfort, hence improving LA experience, especially for young people, to help reduce or avoid dental anxiety development, and to provide a more satisfactory therapeutic experience in itself (Gibson et al., 2000).

The Wand is now used in many dental hospitals as part of the standard care to deliver local anaesthetic for the purpose of performing painless dental treatment. National figures for its uptake do not exist. At the UCLH Eastman Dental Hospital, approximately 20-30% of patients will have the Wand, the remainder conventional syringe. At present use of the Wand is up to the individual operator and availability of the Wand machine, decision to use is entirely subjective and not rooted in any evidence of acceptability etc.

Most present literature in paediatric dentistry about the Wand CCLAD is largely based on perceptions of pain and distress, and its effectiveness in contrast to the traditional syringe. Nonetheless, there is still a degree of ambiguity, as data appears to be conflicting and the quality of various trials is controversial. In some studies, the Wand was found to deliver less painful LA than the conventional syringe (Hochman et al., 1997; Gibson et al., 2000; Palm et al., 2004; Versloot et al., 2005) whereas in others, there was no difference between the two techniques (Asarch et al., 1999; Ram & Peretz, 2002). Additionally, evidence concerning its acceptability among young people is weak, due to the fact that the acceptability of the actual injection techniques has not been assessed. However, it was reported that the overall treatment acceptance was measured (Asarch et al., 1999).

In the systematic review done during the first stage of our research (not yet published at the time of writing this protocol), the literature was searched for randomised controlled trials investigating children’s acceptability of the Wand LA. For the purposes of literature review undertaken in this study of paediatric dentistry, ‘children’ are operationally defined as patients aged under 16. Only two trials were identified measuring children’s acceptance and satisfaction, however, they measured the overall treatment rather that for the Wand LA specifically. In the second stage of this research, the acceptability of the Wand LA was measured qualitatively through in-depth interviewing children following receiving the treatment (not yet published at the time of writing this protocol). The findings of the qualitative study suggest that children commonly find the Wand anaesthetic more acceptable than that of the conventional syringe, in part due to the painless anaesthetic delivery and the non-threatening appearance of the Wand. These two variables will be used to measure the LA acceptability of the Wand compared to the conventional syringe in the following stage of this research. The effect of the LA technique on the anxiety level will also be assessed as a secondary outcome.

This pilot clinical trial will provide sufficient evidence so that a future larger trial can be performed. Children have been involved as patients in the identification of the aspects to be measured to assess the acceptability of the Wand LA. Children were also involved in developing the patient information sheets of this trial and ensuring they are clear and easy to understand for their ages (10-16 yrs.). Scales used in the study were previously developed by children and validated in other studies by other researchers.

## Assessment and management of risk

The table below summarise the risks and mitigations of local dental anaesthesia in current standard care.

|  |  |  |
| --- | --- | --- |
| **Intervention** | **Potential risk** | **Risk Management** |
| Local dental anaesthesia | Swelling, pain, bleeding, adjacent tissue numbness, failure of LA, allergy to LA substance | Performed by trained dentists following trusted, standard operational procedures. |
|   |

# Objectives

To compare young dental patients’ acceptability of the local anaesthetic delivered by the Wand CCLAD to the local anaesthetic delivered by the conventional dental syringe.

# Trial design

A single-site, unblinded parallel randomised controlled pilot trial was designed. The time taken by the intervention will be the normal time taken during the routine dental treatment to perform LA using the Wand, and no follow up is required for the purpose of this trial. The following illustration shows the trial flow.

# Participant selection

## Inclusion criteria

* Paediatric patients aged 10-16 yrs. It is aimed from this trial to insure that it will reflect the opinions of children from different age groups as much as possible, but the dental injection fear rating profile to be used in this trial was validated and found to be reliable specifically for children aged 10-16 years’ old.
* No previous experience of having LA delivered by the Wand.
* Able to understand English sufficiently to complete scales/rating profiles appropriately.
* Patients/parents willing to give informed assent/consent to participate in the study.
* Good general health (American Society of Anaesthesiology ASA classification I & II)
* Co-operative, with no indication for conscious sedation or treatment under general anaesthesia.

## Exclusion criteria

* Aged below 10 or over 16 years’ old.
* Paediatric patients who have previously received dental anaesthesia using the Wand.
* Children who are unable to understand English sufficiently.
* Children with ASA class III or over.
* Pre co-operative or highly anxious who require treatment under conscious sedation or general anaesthesia.
* Parents/participants unable or unwilling to give consent or, parent consent and child not willing to participate.

## Recruitment

Participant recruitment at the site will only commence when the trial has:

1. Been confirmed by the Sponsor (or a delegated representative),
2. Received ethical approval from the Research Ethics Service (REC), and HRA
3. Been issued an “NHS Permission Letter”.

Following obtaining these approvals, patients, who meet the inclusion criteria, will be approached and invited to participate in the study as they attend their appointments at the Paediatric Dental Department at Eastman Dental Hospital and given information leaflets and verbal explanation about the study by Prof. Paul Ashley and Dr. Susan Parekh who are the research supervisors and members of the clinical team at UCLH Eastman.They will be asked to consider whether they want to be involved for at least 24 hrs. The parents/legal guardians and participants will be given the option to respond via email to confirm their child willingness to involve. However, this will not constitute to formal consent. Potential participants who agreed to be involved will be assented and their parents/legal guardians will be consented and then randomised on the day of which they will have their dental treatment to receive LA administered by either the Wand CCLAD or traditional syringe prior to their dental treatment, using an envelope technique. This will also be done by Prof. Paul Ashley and Dr. Susan Parekh along with the investigator Mrs Rema Elhaj-Husian.

## Informed consent

Informed consent should be obtained before participants take part in any activity, especially in healthcare-related research. Research team members (Prof. Paul Ashley, Dr. Susan Parekh and Mrs Rema Elhaj-Husian) will explain the nature and purpose of the study in full to potential participants and their parents/ guardians in order to invite them to give voluntary informed consent to take part. They will be told that they can decide not to take part or withdraw from the study at any time, and that any decisions they make will not affect the quality of care they receive or their statutory rights. Paediatric patients will be assessed when they attend their appointment at either new-patient or treatment clinics in the study setting and will be invited to participate in the trial if they satisfy the inclusion requirements. A detailed verbal explanation and information leaflets will be given to potential participants and their parents/ guardians by Prof. Paul Ashley and Dr. Susan Parekh to allow for sufficient time to consider whether they want to be involved in the trial or not (a minimum of 24 hrs.). If they agree to be included at their next appointment, they can be randomised to receive either the control or the intervention treatment on the same day of the trial.

No trial procedures will be conducted prior to the participant and their parent/guardians giving formal assent/consent by signing the assent/consent form and should the parent consent but the child not want to take part, the child would not be included in the study. Following this, the participants will be enrolled into the trial. A copy of the signed informed assent/consent form will be given to participants and their parents/guardians, while the original signed will be retained in the trial file at site, and a copy will be placed in participants’ medical notes. The participant information sheet and consent form will be reviewed and updated if necessary, throughout the trial (e.g. where new safety information becomes available), and participants will be invited to reaffirm their consent when appropriate.

# Product/ interventions

## Name and description of intervention(s) under investigation

The computer-controlled local anaesthetic device CCLAD Wand was developed by Milestone Scientific™ and was first introduced in 1997. The American Dental Association describes it as a “local anaesthetic delivery system accepted as a device that has been shown to safely and effectively deliver anaesthetic solution when used by an appropriately qualified professional” (Lieberman, 1999). It has been CE marked.

# Trial procedures

## Pre-intervention assessments

The following trial-specific procedures will be carried out after obtaining consent to assess participants’ eligibility.

All pre-treatment procedures will be carried out as specified in the schedule of assessments (Appendix 1).

Patients will be screened for eligibility against the inclusion criteria for their age (10-16 years); their medical history will be checked for any health problems that will interfere with their participation in the trial (ASA Class III or above); and their dental history will be reviewed for any previous experience with local anaesthetic administrated with the Wand. Patients are required to have no previous experience with the Wand LA in order to be eligible. Participants who agree to take part in the study will then be shown and explained how to use the modified Visual Analogue Scale (VAS) before the trial on the same day which will be used by them to assess the LA acceptability during the intervention.

## Randomisation procedures

Following participants’ assent and their parents/guardians’ consent, and confirmation of eligibility (see section 8.1 for pre-treatment assessments), the randomisation procedure described below will be carried out.

Participants are considered to be enrolled into the trial following formal assent/consent. All of the enrolled participants will be assigned to either the intervention or control group. Simple randomisation will be used for the allocation. The randomisation will be conducted via an envelope technique provided by the statistician – the dentist providing the treatment will draw a sealed envelope from a box and open it – this will have the details of which LA technique they are to use for the contingent patient. The researchers will be blinded to the group assignment of participants.

Patients and clinical practitioners who provide dental treatment, including the administration of the LA, will not be blinded during the clinical trial, as it is not possible, nor pertinent to the process. The outcome assessment will be self-reported by patients.

## Intervention procedures

All enrolled children in this trial will follow a three-phase procedure on the trial day as follows. Data will be recorded by the operator providing the treatment:

* **Pre-LA phase:** In this stage participants will indicate their prospective acceptability for the intervention by completing the Children’s Intervention Rating Profile (CIRP), following which pre-LA participants’ anxiety will be recorded using Children’s Experience of Dental Anxiety Measure (CEDAM). It is estimated that this phase will last for 10 minutes.Patients’ anxiety is already assessed routinely as part of standard care. For this study, it will be assessed prior and after receiving local anaesthetic, by completing the Children’s Experiences of Dental Anxiety Measure (CEDAM). This scale was developed by Porritt et al in 2017 with children and found to be valid and reliable. The research team and wider clinical team are familiar with this scale. They will be provided with refamiliarization before this study starts.
* **LA phase:** During this stage the intervention group will receive LA via the Wand whereas the control group will receive LA via the traditional syringe, as a part of their required dental treatment. Treatments will be provided by the same practitioners who ordinarily treat the participants, and who are part of the clinical staff at the hospital. Immediately following the administration of the LA, participants will be given a modified VAS to record their concurrent acceptability of the LA received and this is estimated to take aprox. 1min. Subsequently, the dental treatment will be continued and is estimated to range from 30-60 minutes, depending on the presenting dental complaints of participants. The trial treatments will be applied as a one-off at the Eastman Dental Hospital, and only this visit will be recorded and administered by clinical staff according to a standardised procedure, as blinding will not be feasible. This will be as follows:
	+ Oral mucosa of the injection site will be dried and a topical anaesthetic, Lignocain 5% (a generic drug), will be applied by a cotton applicator for one minute.
	+ LA will be performed according to the site of treatment (infiltration or nerve block) using the same LA substance (2% Lidocain with 1:80,000 epinephrine) and quantity for both types of techniques, as well as the gauge and the length of the needle. The conventional dental syringe will be used to deliver LA to control group participants and the WandTM (Milestone Scientific Inc.) will be used to deliver LA to the intervention group, as per the manufacturers’ instructions. Both are standard devices used in everyday dental treatment provided in the Hospital.
* **Post-LA phase:** Similar to the pre-LA phase, the acceptability and the anxiety of the participants to the LA provided will be measured using the same scales from the pre-LA phase (CEDAM and CIRP), however acceptability in this phase is measured retrospectively. Further, children’s fear of dental injections will be measured with Intra-Oral Injection Fear Scale (IOIFs). This stage will last approximately 15 minutes.

The researcher will not be involved or present during the treatment and the VAS will be provided by the operating dentist during the treatment. The researcher will administer questionnaires pre and post treatment in the waiting area.

## Subsequent assessments and procedures

After the trial visit the trial is complete, and patients will continue with treatment as normal. A schedule of all trial assessments and procedures is presented in Appendix 1.

## Discontinuation/withdrawal of participants

In consenting to participate in the trial, participants are consenting to intervention, assessments, and data collection.

A participant may be withdrawn from trial whenever continued participation is no longer in the participant’s best interests, but the reasons for doing so will be recorded. Reasons for discontinuing the trial may include:

* Change of health condition or inter-current illness
* Patients withdrawing consent

The decision to withdraw a participant from treatment will be recorded in the case report form CRF and medical notes by the chief investigator who is part of the clinical staff at the hospital. If a participant explicitly states that they do not wish to contribute further data to the trial, their decision will be respected and recorded in the CRF and their medical notes by the chief investigator Prof. Paul Ashley who is part of the clinical staff at the hospital. However, the participant and all identifiable data collected (such as consent/assent forms) would be withdrawn from the study. Data which is not identifiable to the research team may be retained.

# Definition of end of trial

The expected duration of the trial is two months from the recruitment of the first participant. The end of trial is the date of the last visit of the last participant.

# Recording and reporting of adverse events

##  Definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| Adverse Event (AE) | Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved.  |
| Serious Adverse Event (SAE) | Any adverse event that:* Results in death
* Is life-threatening\*
* Requires hospitalisation or prolongation of existing hospitalisation\*\*
* Results in persistent or significant disability or incapacity
* Consists of a congenital anomaly or birth defect
 |
| \* A life-threatening event, this 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.\*\* Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE. |
|   |

## Assessments of adverse events

The intervention is part of the routine dental care in the hospital to deliver LA for dental treatment and it is very unlikely that any adverse events will occur, apart from those acknowledged as complications of dental LA. However, each adverse event, if any arise, will be assessed for severity, causality, seriousness, and expectedness, as described below in the general guidance for assessment of adverse events.

### Severity

|  |  |
| --- | --- |
| **Category** | **Definition** |
| Mild | The adverse event does not interfere with the participant’s daily routine, and does not require further intervention; it causes slight discomfort |
| Moderate | The adverse event interferes with some aspects of the participant’s routine, or requires further 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 |
|   |

### Causality

The assessment of relationship of adverse events to the intervention is a clinical decision based on all available information at the time of the completion of the case report form. It is of particular importance in this trial to capture events related to the procedure (e.g. surgery or device). The assessment of relationship of an adverse event to these additional safety issues will also be carried out as part of the trial. The differentiated causality assessments will be captured in the trial specific CRF. The following categories will be used to define the causality of the adverse event:

|  |  |
| --- | --- |
| **Category** | **Definition** |
| *Definitely* | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. |
| *Probably* | 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 administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant events). |
| *Unlikely* | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatments). |
| *Not related* | There is no evidence of any causal relationship. |
| *Not assessable* | Unable to assess on information available. |
|   |

### Expectedness

|  |  |
| --- | --- |
| **Category** | **Definition** |
| *Expected* | An adverse event which is consistent with the information about the intervention listed in the manual of Operation. |
| *Unexpected* | An adverse event which is not consistent with the information about the intervention listed in the manual of Operation |

\* This includes listed events that are more frequently reported or more severe than previously reported.

As part of UCLH policies, the reference document to be used to assess expectedness against the intervention is the *Manual of Operation*. In reference to the *Manual*, the events listed below describe expected procedural related AEs (refer to section 3.1 to see the table of potential risks).

## Recording adverse events

All adverse events will be recorded in the medical records in the first instance. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates, when appropriate.

### Procedures for recording and reporting serious adverse events

All serious adverse events will be recorded in the medical records and the CRF by the chief investigator who is part of the clinical staff at the hospital, and the sponsor’s AE log and will be reported to the sponsor.

All SAEs (except those specified in section 9.5 as not requiring reporting to the sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor’s SAE form and the form will be preferably emailed to the sponsor within five working days of becoming aware of the event. The chief or principal investigator will respond to any SAE queries raised by the sponsor as soon as possible. Where the event is unexpected and thought to be related to the intervention, this must be reported by the investigator to the Health Research Authority within 15 days.

# Flow chart for SAE reporting

**Submit SAE form to sponsor within 24 hours**

**Email forms to** **randd@uclh.nhs.uk**

Record in medical records, CRF (and AE Log if required)

Record in medical records and CRF (if applicable)

No

Yes

Record in medical records and CRF, in accordance with the protocol

**Is the event specified as an adverse event which does not require immediate reporting as an SAE?**

Yes

Yes

No

**Was the event another notifiable event?**

See section 9.5 for notifiable events which should also be reported as serious

No

**Was the event serious?**

**AE occurs**

**Assign severity grade**

## Reporting urgent safety measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than three days from the date the measures are taken, giving written notice to the relevant REC and sponsor of the measures taken and the circumstances giving rise to those measures.

## Notification of reportable protocol violations

 A reportable protocol violation is a breach which is likely to effect to a significant degree:

1. The safety or physical or mental integrity of the participants of the trial; or
2. The scientific value of the trial.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

## Reporting incidents involving a medical device(s)

The device which will be used in the intervention treatment (the Wand) is used in dental practice from approximately 20 years until present and is accepted as a device that has been shown to safely and effectively deliver anaesthetic solution when used by an appropriately qualified professional. It is specifically being used in clinic in Eastman Dental Hospital at UCLH. Nonetheless, any adverse incident involving a medical device should be reported to the manufacturer of the device.

This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.1 for the definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

All adverse incidents must be reported to Wand® Dental, Inc. (a division of Milestone Scientific), 220 South Orange Avenue, Livingston, NJ 07039, Tel.: 0019735352717, E-mail: lkaunitz@milestonescientific.com

Incidents should be reported as soon as possible (usually within 24 hours).

Incidents should be reported to the manufacturer using the form provided.

Adverse incidents related to a medical device can be reported directly to the MHRA via the online system ([www.mhra.gov.uk](http://www.mhra.gov.uk)). Alternative contact details: Medicines & Healthcare products Regulatory Agency Adverse Incident Centre (Tel: 020 7084 3080; Fax 020 7084 3109).

Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and trial site team to ensure they are aware of any specific local requirements for reporting device incidents.

## Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

1. It is an accident or other incident which results in injury or ill health.
2. It is contrary to specified or expected standard of patient care or service.
3. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
4. It puts the Trust in an adverse position with potential loss of reputation.
5. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them. A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

1. It is an accident or other incident which results in injury or ill health.
2. It is contrary to specified or expected standard of patient care or service.
3. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
4. It puts the Trust in an adverse position with potential loss of reputation.
5. It puts Trust property or assets in an adverse position or at risk of loss or damage.

# Data management

## Confidentiality

All data will be handled in accordance with the UK Data Protection Act (2018).

The Case Report Forms (CRFs) will not bear participants’ names or other personal identifiable data and will not leave the Hospital and will be stored in locked cabinet at the CI’s office. The participants’ initials, dates of birth, and trial identification numbers will be used for identification, and this will be clearly explained to the patients in the participant information sheet, with their consent.

## Data collection tools and source document identification

Data will be collected from sites on trial-specific case report forms (CRFs).

Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.

A source document list will be implemented prior to the start of the trial to identify:

* Which data is to be recorded directly onto the CRF;
* Which data is recorded firstly into source documents, such as medical notes, and then transcribed into the CRF; and
* Which data is not to be recorded in the CRF but only recorded in source documents, e.g. participant questionnaires.

It is 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, including those who have access to the trial database.

### Completing case report forms

All CRFs must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI to perform this duty. The CI is responsible for the accuracy of all data reported in the CRF. Once completed the original CRFs will be stored at site in a locked cabinet.

## Data handling

In the study, no identifiable data will be collected from participants and no master list of who has participated in the study will be kept as there will be no follow up required in this research. Intervention acceptability measuring profiles and anxiety scales will be collected from participants in accordance with the participant’s consent form, participant’s information sheet and section 10.1 of this protocol.

The completed outcomes measuring forms will be appropriately sent to the principal investigators:

Rema Elhaj-Husian, Eastman Dental Institute, 256 Gray’s Inn Road, London, WC1X 8LD for data analysis and synthesis of results; UCL will act as the data controller of such data for the study.

Rema Elhaj-Husian, Eastman Dental Institute, 256 Gray’s Inn Road, London, WC1X 8LD will process, store and dispose of the completed forms in accordance with all applicable legal and regulatory requirements, including the UK Data Protection Act 2018, and any amendments thereto. Patient data will be stored centrally in a locked filing cabinet controlled by the chief investigator.

The completed trial outcome measuring forms will not be transferred to any party not identified in this protocol and are not to be processed and/ or transferred other than in accordance with the patients’ consent.

# Statistical considerations

## Primary outcome

The acceptability of the LA delivered during the trial, for the purpose of performing dental treatment required, will be assessed as a primary outcome and compared between the Wand and the traditional syringe. A conceptual definition of acceptability of health care interventions was proposed as “a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention” (Sekhon, Cartwright, & Francis, 2017). In this trial the acceptability is assessed in three points; before, during, and after the treatment, using the CIRP for measuring prospectively and retrospectively and VAS for assessing the outcome during the treatment. These scales have been proven to be reliable for use with children aged 10 years and over (Shields et al., 2003; Turco and Elliott, 1986a,1986b).

## Secondary outcome(s)

Meeting young patients’ expectations and needs by providing more acceptable dental care affects their behaviour and attitudes, and lessens pain and anxiety (Butters & Willis, 2000), which leads to improving their overall health and wellbeing. Participants’ level of anxiety will be measured as a secondary outcome before and after the treatment using CEDAM questionnaire. The anxiety level for each participant after the treatment will then be compared to the one before receiving the treatment and will be co-related to the device used to administrate the LA. Additionally, dental injection fear will be assessed after the treatment using IOIF scale. Scales have been proven to be reliable for use by children aged 10 years and over (Berge et al., 2016; Porritt et al., 2017).

## Sample size calculation

There are no previous similar studies on which to base the sample size calculation. This study is designed as a pilot trial; thus approximately 10-15 patients per group (20-30 in total) or greater is recommended (Hertzog, 2008). As there is no publicly available information on similar trials, it is therefore advised by the statistician that it is not reasonable to conduct a sample size calculation in this case. It is hoped that this pilot trial will, however, yield information that will help with sample size calculations for future similar larger studies. The number of participants will be decided by considering the realistic number of children that could be recruited within the timeframe allocated to the pilot study. Participants will be randomised to intervention or control group with a ratio of 1:1.

## Planned recruitment rate

Participants’ recruitment is expected to last for 30 days. It is estimated that 100 children are seen monthly in the new patients clinics at Eastman Dental Hospital, in addition to another 516 children in the other clinics (*University College London Hospitals*, no date). Giving child dental patients LA with both methods as part of their dental treatment is a common measure therefore, the sample size is attainable in practice.

## Randomisation methods

Participants will be randomised to receive LA for their dental treatment using either control or intervention delivery method following their formal assent and consent were obtained. Simple randomisation will be used and generated using an envelope technique.

## Statistical analysis

### Primary outcome analysis

The primary outcome to be measured is the acceptability of the LA delivered. This will be measured using a rating profile called Children’s Intervention Rating Profile (CIRP) (Witt & Elliott, 1983). This is a validated tool to measure intervention acceptance using seven statements with a six-point Likert-type scale. Concurrent acceptability will be assessed using modified VAS, a 100 mm scale with *extremely not acceptable* description on the left end, and *extremely acceptable* on the right. The acceptability score will be calculated measuring the scale from the left end to the participant’s indicated level of acceptability. The VAS divided into percentages (10mm indicating 10%, 20mm indicting 20%, etc.) and the acceptability estimations are 0-20% *extremely not acceptable*, 21-40% *not acceptable*, 41-60% *acceptable*, 61-80% *very acceptable*, and 81-100% *extremely acceptable*. Both scales are adapted according to the intervention being measured in this trial. The two groups will be compared using the factorial analysis of variance (ANOVA). This method of statistical analysis is used to compare two or more groups in one or more criteria.

### Secondary outcome analysis

Anxiety of participants will be assessed before and after receiving the LA on the same visit using Children’s Experience of Dental Anxiety Measure (CEDAM) and dental injection fear will be measured using Intra-Oral Injection Fear Scale (IOIFs). CEDAM is a reliable and valid child-reported dental anxiety measure comprising 14 points (Porritt et al., 2017). The 12-point IOIFs has been found to be a valid and reliable measure in children aged 10 to 16. Readings will be compared with each other and correlated with the acceptability of the LA methods before and after the exposure, to find out whether the acceptance of the intervention has an effect on the degree of the anxiety. However, the dental intraoral injection fear will only be assessed post operatively using the IOIFs. Analysis will be performed using ANOVA statistical methods.

### Sensitivity and other planned analyses

This is not applicable for pilot trials. As explained previously, pilot trials are used to predict the robustness and sensitivity analysis of the future definitive trials (Bell et al., 2018).

# Record keeping and archiving

From the declaration of the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 years.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated, and those showing whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request. This will be arranged with the research supervisor (CI).

# Oversight Committees

Trial is overseen by Trial Management Group (TMG).

## Trial Management Group (TMG)

The TMG will include the chief investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly every two weeks (as the pilot trial is two months long).

The TMG will review recruitment figures, SAEs, and substantial amendments to the protocol prior to submission to the REC. The PI will be kept informed of substantial amendments.

# Ethical requirements and patient and public involvement

## Ethics

The sponsor will ensure that the trial protocol, participant information sheet, consent form, and submitted supporting documents have been approved by the appropriate research ethics committees, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before any NHS site may be opened to recruit participants, the chief/ principal investigator or designee must receive NHS permission in writing from the Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician’s responsibility to take immediate action if thought necessary to protect the health and interests of individual participants (see section 9.6 for reporting urgent safety measures).

An Annual Progress Report (APR) will be prepared by the chief investigator and submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. However, it is estimated that the trial will only last for 2 months and will be a one-off procedure per each participant.

Within 90 days after the end of the trial, the CI/sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the sponsor with a summary report of the trial, which will then be submitted to the REC within one year after the end of the trial.

## Patient and public involvement (PPI)

In a former stage of the research, a qualitative study was performed wherein participants who met similar inclusion criteria to the ones of this study were interviewed about their acceptability of the Wand CCLAD. One of the aims of the qualitative study was to involve paediatric patients and the young public in development of patient-reported outcome measures (PROMs) for LA injection acceptability. This was achieved through establishing which outcomes to be measured, items generation and checking their validity and comprehension by patients. These were then decided to be assessed with a validated acceptability measuring tool (CIRP) in this trial (the qualitative part of the research) to assess the acceptability of the Wand LA to this particular group of the public and compare it to the LA acceptability of the traditional syringe. Children were also involved in developing the patient information sheets of this trial and ensuring they are clear and easy to understand for their ages (10-16 yrs). Scales used in the study were previously developed by children and validated in other studies by other researchers.

# Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the risks associated with the trial.

A trial-specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

As this study is classified as medium risk, the monitoring plan that will be followed is by central monitoring. Each site (single site in this study at EDI) to email the sponsor twice yearly:

1.            Delegation log

2.            Adverse Event log

3.            Deviation log

4.            Minutes of Trial Steering Committee (or equivalent).

5.            Annual progress report (Lead site only) when sent to Ethics Committee.

# Finance

This study is part of a PhD project that is fully funded by the Libyan Ministry of Higher Education through the Cultural Affairs Office at the Libyan Embassy in London, as the principal investigator is a Libyan-sponsored research student.

# Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the trial*.* Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the Hospital continues to have a duty of care to the participants in the 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 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 trial shall provide 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.

Should participants require any further information, they may contact Jennifer O’Donnell at Jennifer.o’donnell@ucl.ac.uk.

# Publication policy

Results from this study will be published on websites and displayed in posters in the waiting room of the Paediatric Dentistry Department at Eastman Dental and in the PhD thesis. It is also intended to present the findings in conferences.

# Intellectual property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party’s rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights (“IPR”) to UCL and to disclose all such know-how to UCL.

The participating site agrees to, at the request and expense of UCL, execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching, and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

**20. Conflict of interest**

The Chief Investigator and the other members involved in the research have no conflict of interest.

Appendix: Schedule of assessments

|  |  |  |
| --- | --- | --- |
|  | **Screening (pre-treatment assessment)** | **Intervention phase** |
| Visit No: | 1 | 2 |
|  | Day – X to Day -X | Day 1 |
| Informed Consent | X |  |
| Medical History | X |  |
| Eligibility confirmation | X | X |
| Add ALL protocol assessments including intervention, bloods/urine, ECGs, scans, c as applicable both trial specific and routine (include separate row for each assessment) | Baseline information: age, anxiety, location of dental treatment required | * Preoperative anxiety and LA acceptability assessment.
* Concurrent LA acceptability assessment.
* Postoperative anxiety and LA acceptability assessment.
* Postoperative injection fear assessment
 |
| Randomisation  |  | X |
| Adverse Events review | X | X |
|   |

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